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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/26, 9/20, 31/44	A1	(11) International Publication Number: WO 96/01623 (43) International Publication Date: 25 January 1996 (25.01.96)
(21) International Application Number: PCT/SE95/00677 (22) International Filing Date: 7 June 1995 (07.06.95) (30) Priority Data: 9402433-8 8 July 1994 (08.07.94) SE 9402432-0 8 July 1994 (08.07.94) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): BERGSTRAND, Pontus, John, Arvid [SE/SE]; Walleriusgatan 4, S-412 58 Göteborg (SE). LÖVGREN, Kurt, Ingmar [SE/SE]; Violinvägen 2D, S-435 44 Mölnlycke (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG). Published <i>With international search report.</i>
(54) Title: MULTIPLE UNIT TABLETED DOSAGE FORM I (57) Abstract A new pharmaceutical multiple unit tableted dosage form containing omeprazole or one of its single enantiomers or an alkaline salt of omeprazole or one of its single enantiomers, a method for the manufacture of such a formulation, and the use of such a formulation in medicine.		

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MULTIPLE UNIT TABLETED DOSAGE FORM I

Field of the invention.

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The present invention is related to new pharmaceutical preparations in the form of a multiple unit tableted dosage form comprising omeprazole or one of its single enantiomers or an alkaline salt of omeprazole or one of its single enantiomers. The novel tableted dosage form is intended for oral use. Furthermore, the present invention refers to a method for the manufacture of such preparations and, to the use of such preparations in medicine.

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Background of the invention

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The compound known under the generic name omeprazole, 5-methoxy-2[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, is disclosed i.a. in EP-A1-0 005 129. Certain salts of omeprazole including alkaline salts of omeprazole are described in EP-A1- 0 124 495 and in WO 95/01977. Novel salts of the single enantiomers of omeprazole are described in WO 94/27988.

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Omeprazole or one of its single enantiomers or alkaline salts thereof, in the following stated shortly as omeprazole, are useful for inhibiting gastric acid secretion in mammals and man. In a more general sense, said substances may be used for prevention and treatment of gastric acid related diseases in mammals and man, including e.g. reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, omeprazole may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, and in patients with

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gastrinomas. Omeprazole may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre-and postoperatively to prevent acid aspiration of gastric acid and to prevent and treat stress ulceration. Further, omeprazole may be useful in the treatment of psoriasis as well as in the
5 treatment of Helicobacter infections and diseases related to these.

Omeprazole is, however, susceptible to degradation/transformation in acidic and neutral media. The half-life of degradation of omeprazole in water solutions at pH-values less than three is shorter than ten minutes. The degradation of
10 omeprazole is catalyzed by acidic compounds and is stabilized in mixtures with alkaline compounds. The stability of omeprazole is also affected by moisture, heat, organic solvents and to some degree by light.

In respect to the stability properties of omeprazole, it is obvious that omeprazole
15 in an oral solid dosage form must be protected from contact with the acidic gastric juice and the active substance must be transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid absorption of omeprazole can occur.

A pharmaceutical oral dosage form of omeprazole is best protected from contact
20 with acidic gastric juice by an enteric coating layer. In US-A 4,786,505 such an enteric coated omeprazole preparation is described. Said omeprazole preparation contains an alkaline core comprising omeprazole, a separating layer and an enteric coating layer. In order to further enhance the stability during storage the
25 prepared formulation may optionally be packed with a desiccant.

The hard gelatine capsules containing an enteric coated pellet formulation of omeprazole marketed by the Applicant today, are not suitable for press-through blister packages. Thus, there has been a demand for development of new enteric
30 coating layered multiple unit preparations of omeprazole with good chemical stability as well as improved mechanical stability making it possible to produce

well functioning and patient-friendly packages. Furthermore, there is a demand for omeprazole formulations having improved patient acceptance, such as divisible and/or dispersible tablets.

- 5 An improved mechanical stability can be obtained with an enteric coating layered tablet for example as described in WO 95/01783. However, only an enteric coating layered multiple units tablet can be made divisible and dispersible. A further advantage of a multiple unit dosage form is that it disperses into a multitude of small units in the stomach upon administration.

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Prior art discloses many different types of multiple unit dosage forms. Usually this type of formulation is requested for controlled release formulations, such as sustained release formulations. Typically, the multiple unit formulation may be a tablet which disintegrates in the stomach to make available a multitude of coated units, or pellets filled in a capsule. (See for example EP 0 080 341 and US-A 4,786,505).

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An example to obtain a controlled release dosage form releasing the active substance by diffusion through a membrane is described in US-A 4,927,640, i.e. a multiple-unit system containing small inert cores coated with active substance and a release controlling polymeric membrane. The mechanical properties of such multiple units formulated into tablets are reported in *Pharmaceutical Research*, 10 (1993), p.S-274. Other examples of controlled release dosage forms are for example described in Aulton M.E. (Churchill Livingstone), *Pharmaceutics: The science of dosage form design* (1988), p. 316-321.

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Even if the specification of US-A 4,786,505 under the subtitle Final dosage form mentions that the manufactured pellets may be formulated into tablets there are no examples describing any compositions of such a tablet formulation or a technique to manufacture such a formulation. In practice, problems arise when enteric coating layered pellets containing acidic susceptible benzimidazoles as

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active substance are compressed into tablets. If the enteric coating layer does not withstand the compression of the pellets into a tablet the susceptible active substance will be destroyed by penetrating acidic gastric juice, i.e. the acid resistance of the enteric coating layer of the pellets will not be sufficient in the
5 tablet after compression. The above described problems are well illustrated in Reference Examples below.

Further, controlled release tablets from enteric coated particles are described in Drugs Made In Germany, 37 No. 2 (1994), p. 53. The teaching in this reference is
10 that a combination of a methacrylic acid copolymer (L30D-55) and a copolymer of ethyl acrylate and methyl methacrylate (NE30D) is suitable as coating polymers for enteric coated particles compressed into tablets. Reference Example III shows that this recommendation is not applicable when formulating multiple unit
15 tableted dosage forms of the acidic susceptible substance omeprazole. The acid resistance of the pellets compressed into a tablet is too low. The cited reference Drugs Made In Germany also states that the use of the copolymer L30D-55 without the addition of the copolymer NE30D as material for enteric coating layers will result in coated pellets which cannot withstand compression forces used during the tableting process. With reference to this statement it is
20 surprisingly found that pellets covered with L30D-55 according to this invention, see Examples below, are possible to compress into tablets with fulfilled requirements including acceptable acid resistance of the tablet.

The Applicant is not aware of any working example in the prior art of a multiple
25 unit tableted dosage form comprising an acidic susceptible benzimidazole compound, such as omeprazole.

Description of the invention

The Applicant has now surprisingly found that tablets according to the present invention comprising enteric coating layered units containing an acidic
5 susceptible substance in the form of omeprazole or one of its single enantiomers or an alkaline salt thereof can be manufactured by compressing said units into tablets without significantly affecting the properties of the enteric coating layer. As explained above, if the enteric coating layer is damaged during compression of the enteric coating layered units, the acid resistance of said enteric coating layer in
10 the manufactured tablet will not be sufficient, and the manufactured tablets will not fulfill standard requirements on enteric coated articles, such as e.g. those defined in the United States Pharmacopeia, (USP), hereby incorporated in a whole by reference. In the following the expression "omeprazole" is used alternatively with the more complete expression "omeprazole, one of its single enantiomers, an
15 alkaline salt of omeprazole or one of its single enantiomers" for defining the active substance.

One object of the present invention is to provide a pharmaceutical multiple unit tableted dosage form comprising omeprazole or one of its single enantiomers or
20 an alkaline salt of omeprazole or one of its single enantiomers, in which the active substance is in the form of individually enteric coating layered units compressed into a tablet. The enteric coating layer(s) covering the individual units of active substance has properties such that the compression of the units into a tablet does not significantly affect the acid resistance of the individually enteric coating
25 layered units. The active substance is prevented from degradation and dissolution in acidic media and has a good stability during long-term storage. The enteric coating layer covering the individual units disintegrates/dissolves rapidly in near neutral or alkaline media.

30 Another object of the present invention is to provide a pharmaceutical multiple unit tableted dosage form comprising omeprazole or one of its single enantiomers

or an alkaline salt of omeprazole or one of its single enantiomers which is suitable for press-through blister packages and which also has an improved patient acceptance.

- 5 A further object of the present invention is to provide a multiple unit tableted dosage form comprising omeprazole or one of its single enantiomers or an alkaline salt of omeprazole or one of its single enantiomers, which is divisible and easy to handle. The multiple unit tableted dosage form may be dispersed in an aqueous liquid and can be given to patients with swallowing disorders and in
10 pediatrics. Such a suspension of dispersed omeprazole units of appropriate size can be used for oral administration and also for feeding through a naso-gastric tube.

15 Detailed description of the invention.

- The novel multiple unit tableted dosage form comprising omeprazole or one of its single enantiomers or an alkaline salt of omeprazole or one of its single enantiomers is characterized in the following way. Individually enteric coating
20 layered units containing omeprazole or one of its single enantiomers or an alkaline salt of omeprazole or one of its single enantiomers, and optionally alkaline substances, are mixed with tablet excipients and compressed into multiple unit tableted dosage forms. With the expression "individual units" is meant small beads, particles, granules or pellets, in the following referred to as
25 pellets.

- The compaction process (compression) for formulating the multiple unit tableted dosage form must not significantly affect the acid resistance of the enteric coating layered pellets. In other words the mechanical properties, such as the
30 flexibility and hardness as well as the thickness, of the enteric coating layer(s) must secure that the requirements on enteric coated articles in the United States

Pharmacopeia are accomplished and that the acid resistance does not decrease more than 10% during the compression of pellets into tablets.

5 The flexibility/hardness of enteric coating layers can be characterized for instance as Vickers hardness measured with a Shimadzu micro hardness indentation tester type HMV 2 000.

10 The acid resistance is defined as the amount of active substance in tablets or pellets after being exposed to simulated gastric fluid, USP, or to 0.1 M HCl(aq) relative to that of unexposed tablets or pellets, respectively. The test is accomplished in the following way. Tablets or pellets are exposed to simulated gastric fluid at a temperature of 37°C. The tablets disintegrate and release the enteric coating layered pellets to the medium. After two hours the enteric coating layered pellets are removed and analyzed for omeprazole content using High
15 Performance Liquid Chromatography (HPLC). Presented values of acid resistance are averages of at least three individual determinations.

Core material

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The core material for the individually enteric coating layered pellets can be constituted according to different principles. Seeds layered with active substance in the form of omeprazole or one of its single enantiomers or an alkaline salt of omeprazole or one of its single enantiomers, optionally mixed with alkaline
25 reacting compounds, can be used as the core material for the further processing.

The seeds, which are to be layered with the active substance, can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or in mixtures or water soluble seeds comprising different
30 inorganic salts, sugars, non-pareils and other materials, alone or in mixtures. Further, the seeds may comprise active substance in the form of crystals,

agglomerates, compacts etc. The size of the seeds is not essential for the present invention but may vary between approximately 0.1 and 2 mm. The seeds layered with active substance are produced either by powder or solution/suspension layering using for instance granulating or spray coating/layering equipment.

5

Before the seeds are layered, the active substance may be mixed with further components. Such components can be binders, surfactants, fillers, disintegrating agents, alkaline additives or other pharmaceutically acceptable ingredients, alone or in mixtures. The binders are for example celluloses such as hydroxypropyl methylcellulose, hydroxypropyl cellulose and carboxymethyl-cellulose sodium, polyvinyl pyrrolidone, sugars, starches and other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic or ionic surfactants such as for instance sodium lauryl sulfate.

15

Alternatively, omeprazole optionally mixed with alkaline compounds and further mixed with suitable constituents can be formulated into core material. Said core materials may be produced by extrusion/spheronization, balling or compression utilizing different process equipments. The size of the formulated core materials is approximately between 0.1 and 4 mm and preferably between 0.1 and 2 mm. The manufactured core materials can further be layered with additional ingredients comprising active substance and/or be used for further processing.

20

The active substance is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and a suitable concentration of the active substance in the final mixture. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives, can be used.

25

The active substance may also be mixed with an alkaline pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but

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are not restricted to, substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

10

Alternatively, the aforementioned core material can be prepared by using spray drying or spray congealing technique.

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The active substance is in the form of omeprazole or one of its single enantiomers or an alkaline salt of omeprazole or one of its single enantiomers. Omeprazole has an asymmetric centre in the sulfur atom, i.e. exists as two optical isomers (enantiomers). Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixtures of the two enantiomers are suitable for the pharmaceutical formulation according to the present invention. A suitable form of omeprazole for preparation of the new multiple unit tableted dosage form according to the present invention can be the magnesium salt of omeprazole with a specific degree of crystallinity and other physical properties disclosed in WO 95/01977, hereby incorporated in a whole by reference. Said magnesium omeprazole product has a degree of crystallinity which is higher than 70% and preferably higher than 75% as determined by X-ray powder diffraction. Other suitable forms of the active substance are the sodium, potassium, magnesium and calcium salts of the single enantiomers of omeprazole, especially in their crystalline form described in WO 94/27988, hereby incorporated in a whole by reference.

30

Enteric coating layer(s)

Before applying enteric coating layer(s) onto the core material in the form of individual pellets, said pellets may optionally be covered with one or more
5 separating layers comprising pharmaceutical excipients optionally including alkaline compounds such as for instance pH-buffering compounds. This/these separating layer(s) separate(s) the core material from the outer layer(s) being enteric coating layer(s).

10 The separating layer(s) can be applied to the core material by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating process. As an alternative the separating layer(s) can be applied to the core
15 material by using powder coating technique. The materials for separating layers are pharmaceutically acceptable compounds such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking
20 and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be included into the separating layer(s).

When the optional separating layer(s) is applied to the core material it may constitute a variable thickness. The maximum thickness of the optional separating
25 layer(s) is normally only limited by processing conditions. The separating layer(s) may serve as a diffusion barrier and may act as a pH-buffering zone. The pH-buffering properties of the separating layer(s) can be further strengthened by introducing into the layer(s) substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide,
30 hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance

$\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$, aluminium hydroxide/sodium bicarbonate coprecipitate or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of

5 phosphoric, carbonic, citric or other suitable, weak, inorganic or organic acids; or suitable organic bases, including basic amino acids and salts thereof. Talc or other compounds may be added to increase the thickness of the layer(s) and thereby strengthen the diffusion barrier. The optionally applied separating layer(s) is not essential for the invention. However the separating layer(s) may improve the

10 chemical stability of the active substance and/or the physical properties of the novel multiple unit tableted dosage form.

One or more enteric coating layers are applied onto the core material or onto the core material covered with separating layer(s) by using a suitable coating

15 technique. The enteric coating layer material may be dispersed or dissolved in either water or in suitable organic solvents. As enteric coating layer polymers one or more, separately or in combination, of the following can be used; e.g. solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate

20 succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating layer polymer(s).

The enteric coating layers contain pharmaceutically acceptable plasticizers to

25 obtain the desired mechanical properties, such as flexibility and hardness of the enteric coating layers. Such plasticizers are for instance, but not restricted to, triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or other plasticizers.

30 The amount of plasticizer is optimized for each enteric coating layer formula, in relation to selected enteric coating layer polymer(s), selected plasticizer(s) and the

applied amount of said polymer(s), in such a way that the mechanical properties, i.e. flexibility and hardness of the enteric coating layer(s), for instance exemplified as Vickers hardness, are adjusted so that the acid resistance of the pellets covered with enteric coating layer(s) does not decrease significantly during the
5 compression of pellets into tablets. The amount of plasticizer is usually above 10 % by weight of the enteric coating layer polymer(s), preferably 15 - 50 %, and more preferably 20 - 50 %. Additives such as dispersants, colorants, pigments, polymers e.g. poly(ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be included into the enteric coating layer(s). Other
10 compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acid susceptible material.

To protect an acidic susceptible substance in the form of omeprazole or one of its single enantiomers or an alkaline salt of omeprazole or one of its single
15 enantiomers and to obtain an acceptable acid resistance of the multiple unit tableted dosage form according to the invention, the enteric coating layer(s) constitutes a thickness of approximately at least 10 μm , preferably more than 20 μm . The maximum thickness of the applied enteric coating layer(s) is normally only limited by processing conditions.

20

Over-coating layer

Pellets covered with enteric coating layer(s) may further be covered with one or
25 more over-coating layer(s). The over-coating layer(s) can be applied to the enteric coating layered pellets by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating or layering process. The materials for over-coating layers are chosen among pharmaceutically acceptable compounds
30 such as, for instance sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose,

ethylcellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be included into the over-coating layer(s). Said over-coating layer may further prevent potential agglomeration of enteric coating layered pellets, further protect the enteric coating layer towards cracking during the compaction process and enhance the tableting process. The maximum thickness of the applied over-coating layer(s) is normally only limited by processing conditions.

Tablets

The enteric coating layered pellets are mixed with tablet excipients and compressed into a multiple unit tableted dosage form according to the present invention. The enteric coating layered pellets with or without an over-coating layer are mixed with tablet excipients such as fillers, binders, disintegrants, lubricants and other pharmaceutically acceptable additives and compressed into tablets. The compressed tablet is optionally covered with filmforming agent(s) to obtain a smooth surface of the tablet and further enhance the stability of the tablet during packaging and transport. Such a tablet coating layer may further comprise additives like anti-tacking agents, colorants and pigments or other additives to obtain a tablet of good appearance.

The amount of enteric coating layered pellets constitutes less than 75% by weight of the total tablet weight and preferably less than 60 %. By choosing small enteric coating layered pellets in the formulation according to the present invention, the number of pellets in each tablet can be held high which in turn makes the tablet divisible with retained dosing accuracy.

The mechanical properties, i.e. the flexibility and hardness of the enteric coating layer are essential for the acid resistance of the multiple unit tableted dosage form. The flexibility/hardness of the enteric coating layer surface may be characterized as a preliminary process parameter in the form of Vickers hardness, measured on enteric coating layered pellet(s) before compression of said pellets into tablets. The Vickers hardness may be measured with a Shimadzu micro hardness indentation tester type HMV 2000 (Micro Hardness Testing Machines for Vickers and Knoop Hardness JIS B 7734-1984 and JIS Z 2251-1980). The ability of the enteric coating layer(s) to withstand compression into tablets is, of course, a function of both the amount of applied coating layer and the mechanical properties of said coating material. To obtain well functioning enteric coating layered pellets with a reasonable amount of enteric coating layer material and which pellets can be compressed into tablets without significantly affecting the acid resistance, an enteric coating layer surface with a Vickers hardness of less than 8 is preferred. In case the pellets are covered with an over-coating layer the Vickers hardness of the enteric coating layer must be characterized before the over-coating layer is applied. A harder over-coating layer (Vickers hardness higher than 8) can be applied on top of a flexible and softer (Vickers hardness less than 8) enteric coating layer with retained acid resistance during compaction.

Thus, the formulation according to the invention consists of core material containing active substance in the form of omeprazole or one of its single enantiomers or an alkaline salt of omeprazole or one of its single enantiomers, optionally mixed with alkaline compound(s), and excipients. The addition of an alkaline material may not be necessary, but such a substance may further enhance the stability of the active substance. The core material is optionally covered with one or more separating layer(s) optionally containing alkaline substance(s). The pellets, optionally covered with a separating layer(s), are then covered with one or more enteric coating layer(s) making the pellets insoluble in acidic media, but disintegrating/dissolving in near neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, the

site where dissolution is wanted. The enteric coating layered pellets may further be covered with an over-coating layer before being formulated into the multiple unit tableted dosage form.

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Process

The process for the manufacture of the dosage form represents a further aspect of the invention. The pharmaceutical processes can preferably be completely water-based and there are different descriptions given in the accompanying examples below.

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Use of preparation

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The preparation according to the invention is especially advantageous in reducing gastric acid secretion. Such a multiple unit tableted dosage form is administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and the disease. In general the daily dose will be in the range of 1-400 mg of active substance, i.e. omeprazole or one of its single enantiomers or alkaline salts thereof.

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The preparation according to the present invention is also suitable for dispersion in an aqueous liquid with neutral or slightly acidic pH-value before being orally administered or fed through a naso-gastric tube.

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Multiple unit tableted dosage forms of omeprazole according to the present invention have been tested in humans.

The invention is illustrated more in detail by the following examples.

5

EXAMPLES

Example 1

10

Core material

	Magnesium omeprazole	600 g
	Mannitol	1000 g
	Microcrystalline cellulose	300 g
15	Hydroxypropyl cellulose	100 g
	Sodium lauryl sulfate	6 g
	Purified water	802 g

Separating layer

20	Core material	400 g
	Hydroxypropyl methylcellulose	48 g
	Purified water	960 g

Enteric coating layer

25	Pellets covered with separating layer	200 g
	Methacrylic acid copolymer	100 g
	Triethyl citrate	30 g
	Mono- and diglycerides	5 g
	Polysorbate 80	0.5 g
30	Purified water	309 g

Tablets

	Enteric coating layered pellets	200 g
	Microcrystalline cellulose	299 g
35	Sodium stearyl fumarate	1.2 g

Sodium lauryl sulfate is dissolved in purified water to form the granulation liquid. Magnesium omeprazole, mannitol, microcrystalline cellulose and hydroxypropyl cellulose are dry-mixed. The granulation liquid is added to the powder mixture and the mass is wet-mixed.

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The wet mass is forced through an extruder equipped with screens, aperture size 0.5 mm. The extrudate is spheronized on a friction plate in a spheronizing apparatus. The core material is dried in a fluid bed dryer and classified. The prepared core material is covered with separating layer in a fluid bed apparatus with a hydroxypropyl methylcellulose/water solution.

10

The enteric coating layer is applied to the pellets covered with separating layer from an aqueous dispersion of methacrylic acid copolymer plasticized with triethyl citrate to which a mono- and diglycerides/polysorbate dispersion has been added. The pellets are dried in a fluid bed apparatus. The Vickers hardness of enteric coating layered pellets prepared is measured to a value of 2.

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Enteric coating layered pellets, microcrystalline cellulose and sodium stearyl fumarate are mixed and compressed into tablets with a tablet weight corresponding to 20 mg omeprazole, using a single punch tableting machine equipped with 10 mm round punches. Tablets with a hardness of 110 - 120 N (Schleuniger hardness tester) are produced.

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Example 2

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Core material

Magnesium omeprazole	15.0 kg
Sugar sphere seeds	15.0 kg
Hydroxypropyl methylcellulose	2.25 kg
Purified water	40 kg

30

Separating layer

Core material	15.00 kg
Hydroxypropyl cellulose	1.50 kg
Talc	2.57 kg
Magnesium stearate	0.21 kg
Purified water	30 kg

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Enteric coating layer

	Pellets covered with separating layer	18.00 kg
	Methacrylic acid copolymer	9.00 kg
	Triethyl citrate	2.70 kg
5	Mono- and diglycerides	0.45 kg
	Polysorbate 80	0.04 kg
	Purified water	19 kg

Tablets

	Enteric coating layered pellets	6.00 kg
	Microcrystalline cellulose	13.95 kg
	Sodium stearyl fumarate	0.05 kg

10 Suspension layering is performed in a fluid bed apparatus using bottom spray technique. Magnesium omeprazole is sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder. The size of sugar sphere seeds are in the range of 0.25 to 0.35 mm.

The prepared core material is covered with separating layer in a fluid bed
 15 apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethyl citrate and polysorbate is sprayed as a dispersion onto the pellets covered with separating layer in a fluid bed apparatus. The Vickers hardness on enteric coating layered pellets prepared is
 20 measured to a value of 2.

The enteric coating layered pellets are classified by sieving. Enteric coating layered pellets, microcrystalline cellulose and sodium stearyl fumarate are mixed and compressed into tablets using a rotary tableting machine equipped with 36 pairs of 8 mm round punches. The amount of omeprazole in each tablet is approx.
 25 10 mg, tableting speed 110 000 tablets per hour and an upper punch force of 10 kN is used. Tablet hardness measured on a Schleuniger hardness tester is 55 - 65 N.

Example 3

30

Core material

	Magnesium omeprazole	1 500 g
	Sugar sphere seeds (non-pareils)	1 500 g

	Hydroxypropyl methylcellulose	420 g
	Colloidal silicon dioxide	8 g
	Purified water	4 230 g
5	<u>Separating layer</u>	
	Core material	500 g
	Hydroxypropyl cellulose	40 g
	Talc	67 g
	Magnesium stearate	6 g
10	Purified water	800 g
	<u>Enteric coating layer</u>	
	Pellets covered with separating layer	500 g
	Methacrylic acid copolymer	200 g
15	Triethyl citrate	60 g
	Purified water	392 g
	<u>Tablets</u>	
	Enteric coating layered pellets	430 g
20	Microcrystalline cellulose	871 g
	Sodium stearyl fumarate	3 g
25	Magnesium omeprazole, part of the hydroxypropyl methylcellulose and colloidal silicon dioxide are dry-mixed forming a powder mixture. Sugar sphere seeds (0.25-0.35 mm) are layered with the powder in a centrifugal fluidized coating granulator while spraying a hydroxypropyl methylcellulose solution (6 %, w/w).	
30	The prepared core material is dried and covered with separating layer in a centrifugal fluidized coating granulator. A fluid bed apparatus is used for enteric coating layering.	
35	Enteric coating layered pellets, microcrystalline cellulose and sodium stearyl fumarate are mixed and compressed into tablets using a rotary tableting machine equipped with 6 pairs of 10 mm round punches. The amount of omeprazole is approx. 20 mg. Hardness of prepared tablets measured on a Schleuniger hardness tester is determined to 130 - 140 N.	

Example 4Core material

	Magnesium omeprazole	8.00 kg
5	Silicon dioxide seeds	8.00 kg
	Hydroxypropyl methylcellulose	1.41 kg
	Sodium lauryl sulfate	0.08 kg
	Purified water	28 kg

10 Separating layer

	Core material	10.00 kg
	Hydroxypropyl methylcellulose	0.80 kg
	Purified water	10 kg

15 Enteric coating layer

	Pellets covered with separating layer	300 g
	Methacrylic acid copolymer	124 g
	Polyethylene glycol 400	25 g
	Mono- and diglycerides	3 g
20	Polysorbate 80	1 g
	Purified water	463 g

Tablets

	Enteric coating layered pellets	200 g
25	Microcrystalline cellulose	598 g
	Sodium stearyl fumarate	2 g

Suspension layering is performed in a fluid bed apparatus. Magnesium omeprazole is sprayed onto the seeds of silicon dioxide (size range 0.15 - 0.3 mm) from a water suspension containing the dissolved binder and a surface active ingredient.

The prepared core material is covered with separating layer in a fluid bed apparatus using a hydroxypropyl methylcellulose solution. The enteric coating layer material is sprayed as a water dispersion onto pellets in a fluid bed apparatus. The Vicker hardness on enteric coating layered pellets is measured to a value of 3.

Enteric coating layered pellets and the tableting excipients are mixed and compressed into tablets as described in Example 1.

Example 5

5

Enteric coating layer

Pellets covered with separating layer (manufacturing and composition as in Example 1)

		500 g
	Methacrylic acid copolymer	250 g
10	Polyethylene glycol 6000	75 g
	Mono- and diglycerides	12.5 g
	Polysorbate 80	1.2 g
	Purified water	490 g

15

Tablets

	Enteric coating layered pellets	600 g
	Microcrystalline cellulose	1 395 g
	Sodium stearyl fumarate	5 g

20 Enteric coating layered pellets with a measured Vickers value of 2, microcrystalline cellulose and sodium stearyl fumarate are mixed and compressed into tablets as described in Example 3.

Example 6

25

Enteric coating layer

Pellets covered with separating layer (manufacturing and composition as in Example 2)

		500 g
	Hydroxypropyl methylcellulose phthalate	400 g
30	Diethyl phthalate	80g
	Ethanol	1 600 g
	Acetone	4 000 g

Tablets

35	Enteric coating layered pellets	500 g
	Microcrystalline cellulose	1 500 g
	Magnesium stearate	5 g

Enteric coating layering is performed by spaying a solution in a fluid bed. Enteric coating layered pellets, microcrystalline cellulose and magnesium stearate are mixed and compressed into tablets as in Example 3.

5 Example 7

Tablets

Enteric coating layered pellets (manufacturing and composition as in Example 2)

		1.00 kg
10	Dibasic calcium phosphate anhydrous	1.76 kg
	Microcrystalline cellulose	0.44 kg
	Magnesium stearate	0.016 kg

15 Enteric coating layered pellets, dibasic calcium phosphate anhydrous in granulated form, microcrystalline cellulose and magnesium stearate are mixed and compressed into tablets as described in Example 3. Upper punch force is set to approx. 30 kN.

Example 8

20

Core material

	(-)-Omeprazole	600 g
	Sugar sphere seeds	300 g
	Povidone	100 g
25	Purified water	2000 g

Enteric coating layer

	Core material	600 g
	Methacrylic acid copolymer	400 g
30	Triethyl citrate	120 g
	Talc	120 g

Tablets

	Enteric coating layered pellets	1 000 g
35	Microcrystalline cellulose	1 450 g
	Anhydrous lactose	140 g
	Starch	230 g

Povidone	180 g
Purified water	836 g

(-)-Omeprazole is sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder in a fluid bed apparatus.

The enteric coating layer consisting of methacrylic acid copolymer, triethyl citrate and talc is sprayed as a dispersion onto the core material in a fluid bed apparatus.

The tablet excipient povidone is dissolved in water. Microcrystalline cellulose, anhydrous lactose and starch are dry-mixed. The povidone solution is added while wet-mixing. The wet mass is dried in an oven. The granulated mass is milled using an oscillating granulator.

Enteric coating layered pellets and the prepared granulate are mixed and compressed into engraved and scored tablets using a rotary tableting machine equipped with 16 pairs of oval, 8.5x17 mm, tablet punches.

Example 9

Over-coating layer

Enteric coating layered pellets (manufacturing and composition as in Example 2)

Hydroxypropyl methylcellulose	400 g
Purified water	120 g
	2 280 g

Tablets

Over-coating layered pellets	100 g
Microcrystalline cellulose	233 g

In a fluid bed apparatus a hydroxypropyl methylcellulose solution is sprayed onto enteric coating layered pellets. Vickers hardness measured on the enteric coating layered pellets before applying the over-coating layer is determined to 2 and the Vickers hardness measured on the over-coating layered pellets is determined to 11. Pellets covered with over-coating layer and microcrystalline cellulose are mixed and compressed into tablets as in Example 1. Hardness of tablets measured on a Schleuniger tablet hardness tester is determined to 170 - 190 N.

Example 10Core material

	Omeprazole	225 g
5	Mannitol	1425 g
	Hydroxypropyl cellulose	60 g
	Microcrystalline cellulose	40 g
	Anhydrous lactose	80 g
	Sodium lauryl sulfate	5 g
10	Dibasic sodium phosphate dihydrate	8 g
	Purified water	350 g

Separating layer

	Core material	300 g
15	Hydroxypropyl cellulose	30 g
	Talc	51 g
	Magnesium stearate	4 g
	Water	600 g

20 Enteric coating layer

	Pellets covered with separating layer	279 g
	Methacrylic acid copolymer	140 g
	Triethyl citrate	42 g
	Mono- and diglycerides	7 g
25	Polysorbate 80	0.7 g
	Water	300 g

Tablets

	Enteric coating layered pellets	352 g
30	Microcrystalline cellulose	1 052 g
	Sodium stearyl fumarate	3 g

The dry ingredients for producing the core material are well mixed in a mixer. The granulation liquid is added and the mixture is kneaded and granulated to a proper consistency. The wet mass is pressed through an extruder screen. The granules are converted into a spherical form in a spheronizer. The core material is dried in a fluid bed apparatus and classified into a suitable particle size range, 0.7 - 1.0 mm.

Prepared core material is covered with separating layer and enteric coating layer as in Example 2. Enteric coating layered pellets, microcrystalline cellulose and sodium stearyl fumarate are mixed and compressed into tablets as described in Example 3.

5

Example 11

Enteric coating layer

	Core material (no separating layer)	500 g
10	Methacrylic acid copolymer	500 g
	Triethyl citrate	150 g
	Mono- and diglycerides	25 g
	Polysorbate 80	2.5 g
	Purified water	978 g

15

Tablets

	Enteric coating layered pellets	800 g
	Microcrystalline cellulose	1 860 g
20	Sodium stearyl fumarate	7 g

Core material is produced as in Example 2.

Enteric coating layered pellets and tablet excipients are compressed as described in Example 3. The dose of omeprazol in each tablet corresponds to 20 mg. Measured tablet hardness is 80 - 100 N.

25

Example 12

Core material

30	Sodium omeprazole	326 g
	Sugar sphere seeds	300 g
	Hydroxypropyl cellulose	80 g
	Purified water	1 520 g

Separating layer

35	Core material	300 g
	Hydroxypropyl cellulose	21 g

Talc	37 g
Magnesium stearate	5 g
Purified water	400 g

5 Enteric coating layer

Pellets covered with separating layer	270 g
Methacrylic acid copolymer	256 g
Polyethylene glycol 400	64 g
Purified water	1 217 g

10

Tablets

Enteric coating layered pellets	100 g
Microcrystalline cellulose	200 g
Sodium stearyl fumarate	1 g

To produce core material, solution layering is performed in a fluid bed apparatus. Sodium omeprazole is sprayed onto sugar sphere seeds from a water solution containing the dissolved binder.

15

The prepared core material is covered with separating layer in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer material is sprayed as a dispersion onto the pellets covered with separating layer in a fluid bed apparatus.

20

Enteric coating layered pellets and tablet excipients are compressed into tablets as described in Example 1. The amount of sodium omeprazole in each tablet is approx. 15 mg.

25 Example 13

Core material

Magnesium omeprazole	15.0 kg
Sugar sphere seeds (0.25 - 0.35 mm)	15.0 kg
Hydroxypropyl methylcellulose	2.25 kg
Purified water	45 kg

30

Separating layer

	Core material	30.0 kg
	Hydroxypropyl cellulose	3.00 kg
	Talc	5.14 kg
5	Magnesium stearate	0.43 kg
	Purified water	60 kg

Enteric coating layer

	Pellets covered with separating layer	200 g
10	Hydroxypropyl methylcellulose acetate succinate	100 g
	Triethyl citrate	30 g
	Purified water	309 g
	Ethanol	720 g

15 Tablets

	Enteric coating layered pellets	100 g
	Microcrystalline cellulose	227 g
	Crospovidone	5 g
	Sodium stearyl fumarate	1 g

The pellets covered with separating layer are produced as in Example 2.

The enteric coating layer is applied in a fluid bed from a water/ethanol solution.

The Vickers hardness of the enteric coating layered pellets is measured to a value of 5. Enteric coating layered pellets and tablet excipients are mixed and

20 compressed into tablets as described in Example 1.

Example 14Enteric coating layer

25	Pellets covered with separating layer	200 g
	Methacrylic acid copolymer	200 g
	Triethyl citrate	60 g
	Mono- and diglycerides	10 g
	Polysorbate 80	1 g
30	Purified water	391 g

Over-coating layer

	Enteric coating layered pellets	471 g
	Hydroxypropyl methylcellulose	6 g
	Magnesium stearate	0.2 g
5	Purified water	120 g

Tablets

	Over-coating layered pellets	140 g
	Microcrystalline cellulose	114 g
10	Sodium stearyl fumarate	0.4 g

- Pellets covered with separating layer are produced according to Example 13.
The enteric coating layer and the over-coating layer are sprayed onto pellets in a fluid bed apparatus. Over-coating layered pellets and tablet excipients are
15 compressed using a single punch (round, 12 mm) tableting machine.

Example 15Enteric coating layer

20	Pellets covered with separating layer	200 g
	Methacrylic acid copolymer	40 g
	Triethyl citrate	12 g
	Mono- and diglycerides	2 g
	Polysorbate 80	0.2 g
25	Purified water	78 g

Over-coating layer

	Enteric coating layered pellets	200 g
	Hydroxypropyl methylcellulose	4 g
30	Magnesium stearate	0.1 g

Tablets

	Over-coating layered pellets	69 g
	Microcrystalline cellulose	230 g
35	Sodium stearyl fumarate	0.7 g

Pellets covered with separating layer are produced according to Example 13.

The enteric coating layer and the over-coating layer are sprayed onto pellets in a fluid bed apparatus. The amount of enteric coating layer material corresponds to an enteric coating layer thickness of approx. 20 μm . Over-coating layered pellets and tablet excipients are compressed using a single punch (round, 10 mm) tableting machine. Tablet weight approx. 332 mg, and hardness 70 - 77 N.

Example 16

10 Core material

(-)-omeprazole magnesium	300 g
Sugar sphere seeds	300 g
Hydroxypropyl methylcellulose	75 g
Purified water	1 425 g

15

Separating layer

Core material	295 g
Hydroxypropyl cellulose	29.5 g
Talc	50.6 g
20 Magnesium stearate	4.2 g
Purified water	590 g

Enteric coating layer

Pellets covered with separating layer	300 g
25 Methacrylic acid copolymer	120 g
Triethyl citrate	36 g
Mono- and diglycerides	6 g
Polysorbate 80	0.6 g
Purified water	235 g

30

Tablets

Enteric coating layered pellets	150 g
Microcrystalline cellulose	342 g
Crospovidone	7 g
Sodium stearyl fumarate	0.7 g

The enteric coating layered pellets are produced in a fluid bed apparatus. Enteric coating layered pellets and tablet excipients are mixed and compressed into tablets as described in Example 1.

5 Example 17

Enteric coating layer

	Pellets covered with separating layer	500 g
	Cellulose acetate phthalate	375 g
10	Diethyl phthalate	150 g
	Acetone	2 000 g
	Ethanol	2 000 g

Over-coating layer

15	Enteric coating layered pellets	500 g
	Povidone	10 g
	Purified water	200 g

Tablets

	Over-coating layered pellets	100 g
	Microcrystalline cellulose	300 g
	Crospovidone	8 g
	Sodium stearyl fumarate	1 g

20 The pellets covered with separating layer are produced as in Example 2.

The enteric coating layer is applied in a fluid bed from an acetone/ethanol solution. Over-coating layered pellets and tablet excipients are mixed and compressed into tablets as described in Example 1.

25 The results from tests on acid resistance of the enteric coating layered pellets and the compressed tablets are disclosed in Table I, below.

Table I

Example No	Acid resistance, pellets (%)	Acid resistance, tablets (%)
1	91	90
2	99	96
3	96	90
4	91	90
5	94	96
7	95	97
9	96	95
10	97	88
11	94	93
13	98	95
14	99	95
15	98	94
16	97	94

Comments:

- 5 Surprisingly, the acid resistance, tablets, shows that the enteric coating layer according to the present invention sufficiently withstands compression.

Example 7. Due to poor compressability the punch force has to be set very high. Surprisingly there is no reduction in acid resistance after compression.

10

Reference example ITablets

- | | |
|--|-------|
| Omeprazole enteric coating layered pellets | 180 g |
| 15 Microcrystalline cellulose | 219 g |
| Sodium stearyl fumarate | 1 g |

- 20 Omeprazole pellets from Losec® 40 mg capsules are mixed with microcrystalline cellulose and sodium stearyl fumarate and compressed into tablets using a single punch tableting machine. The Vickers hardness on the enteric coating layered pellets is measured to a value of 22. The tablet tooling is round with a diameter of 10 mm. Punch force is set to 3.7 kN.

Reference example IITablets

	Lansoprazole enteric coating layered pellets	276 g
5	(content of Lanzo® 30 mg capsules)	
	Microcrystalline cellulose	644 g

Lansoprazole pellets are mixed with microcrystalline cellulose and tableted in a single punch tableting machine. The Vickers hardness on enteric coating layered pellets is measured to a value of 18. The tablet tooling is round with a diameter of 12 mm. Punch force is set to 3.6 kN.

Reference example III15 Core material

	Magnesium omeprazole	15.0 kg
	Sugar sphere seeds	15.0 kg
	Hydroxypropyl methylcellulose	2.25 kg
	Purified water	40 kg

20

Separating layer

	Core material	15.0 kg
	Hydroxypropyl cellulose	1.5 kg
	Talc	2.57 kg
25	Magnesium stearate	0.21 kg
	Purified water	30 kg

Enteric coating layer

	Pellets covered with separating layer	200 g
30	Enteric coating layer material is used as described in Drugs Made In Germany 37, No. 2 (1994), p.53, Table 1, Formulation no. 9.	
	The amount of coating polymer as calculated in above reference is 40 % (w/w).	

35 Over-coating layer

	Enteric coating layered pellets	291 g
	Hydroxypropyl methylcellulose	4 g

Magnesium stearate	0.2 g
Purified water	80 g

Tablets

5	Over-coating layered pellets	75 g
	Microcrystalline cellulose	174 g
	Sodium stearyl fumarate	0.6 g

- Suspension layering is performed in a fluid bed apparatus. Omeprazol
- 10 magnesium is sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder. The separating layer, enteric coating layer and the over-coating layer are sprayed onto pellets in a fluid bed apparatus. The over-coating layer is applied to prevent sticking of pellets before tableting. Over-coating layered pellets and tablet excipients are tableted as in Example 1. Upper
- 15 punch force is set to 5 kN.

The results from tests on acid resistance of the enteric coating layered pellets and the compressed tablets are disclosed in Table II, below.

20 Table II

Reference example number	Acid resistance pellets (%),	Acid resistance tablets (%),
I	97	6
II	98	25
III	98	82

Comments:

- 25 As can be seen from the presented data, the enteric coating layer of the products studied, including the two marketed products (Reference examples I and II) do not possess the mechanical properties required to withstand compression into tablets.

Preparation of active substance

Magnesium omeprazole used in some of the Examples is produced in accordance with the process given in WO 95/01977, cited above. Omeprazole used in
5 Example 10 is disclosed in EP-A1-0005129, hereby incorporated in a whole by reference. Sodium omeprazole sodium used in Example 12 is disclosed in EP-AI-0124495, hereby incorporated in a whole as reference. The single enantiomers of omeprazole salts used for instance in Example 16, are produced in accordance with the processes given in WO 94/27988, cited above and preferably as described
10 in Examples A and B below.

Example A. Preparation of (-)-omeprazole magnesium salt

Magnesium (0.11g, 4.5 mmol) was dissolved and reacted with methanol (50 ml) at
15 40°C with a catalytic amount of methylene chloride. The reaction was run under nitrogen and was finished after five hours. At room temperature a mixture of the two enantiomers [90%(-)-isomer and 10%(+)-isomer] of 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (2.84 g, 8.2 mmol) was added to the magnesium methoxide solution. The mixture was stirred
20 for 12 hours whereupon a small amount of water (0.1 ml) was added in order to precipitate inorganic magnesium salts. After 30 minutes stirring, these inorganic salts were filtered off and the solution was concentrated on a rotavapor. The residue was now a concentrated methanolic solution of the enantiomeric mixture (i.e. the title compound contaminated with the (+)-isomer), with an optical purity
25 (enantiomeric excess, e.e.) of 80%. This mixture was diluted with acetone (100 ml) and after stirring at room temperature for 15 minutes, a white precipitate was obtained. Additional stirring for 15 minutes and thereafter filtration afforded 1.3 g (50%) of the title compound as white crystals. Chiral analyses of the crystals and mother liquor were performed by chromatography on an analytical chiral column.
30 The optical purity of the crystals and mother liquor was found to be 98.4 e.e. and 64.4% e.e., respectively. Thus, the optical purity (e.e.) has been enhanced from

80% to 98.4% simply by crystallising the Mg-salt from a mixture of acetone and methanol. The product was crystalline as shown by powder X-ray diffraction and the magnesium content was 3.44% as shown by atomic absorption spectroscopy. $[\alpha]_D^{20} = -131.5^\circ$ (c=0.5%, methanol).

5

Example B. Preparation of (+)-omeprazole magnesium salt.

Magnesium (0.11g, 4.5 mmol) was dissolved and reacted with methanol (50 ml) at 40°C with a catalytic amount of methylene chloride. The reaction was run under
10 nitrogen and was finished after five hours. At room temperature a mixture of the two enantiomers [90%(+)-isomer and 10%(-)-isomer] of 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (2.84g, 8.2 mmol) was added to the magnesium methoxide solution. The mixture was stirred for 12 hours whereupon a small amount of water (0.1 ml) was added in
15 order to precipitate inorganic magnesium salts. After 30 minutes stirring, these inorganic salts were filtered off and the solution was concentrated on a rotavapor. The residue was now a concentrated methanolic solution of the enantiomeric mixture (i.e. the title compound contaminated with the (-)-isomer), with an optical purity (e.e.) of 80%. This mixture was diluted with acetone (100 ml) and after
20 stirring at room temperature for one hour, a white precipitate was obtained. Additional stirring for 30 minutes and thereafter filtration afforded 0.35 g of the title compound as white crystals. Additional stirring of the mother liquor for 24 hours at room temperature afforded another 1.0 g (total yield=52%). Chiral analyses of the crystals and the second mother liquor were performed by
25 chromatography on an analytical chiral column. The optical purity of the first crystals was 98.8% e.e. and 99.5% e.e., respectively. The optical purity of the mother liquor was found to be 57% e.e. Thus, the optical purity (e.e.) has been enhanced from 80% to approximately 99% simply by crystallising the Mg-salt from a mixture of acetone and methanol. The first precipitation was crystalline as
30 shown by powder X-ray diffraction and the magnesium content of the same

fraction was 3.49% as shown by atomic absorption spectroscopy. $[\alpha]_D^{20} = +135.6^\circ$
(c=0.5%, methanol).

CLAIMS

1. An oral pharmaceutical multiple unit tableted dosage form comprising tablet excipients and individually enteric coating layered units of a core material
5 containing active substance in the form of omeprazole or one of its single enantiomers or an alkaline salt of omeprazole or one of its single enantiomers, optionally mixed with alkaline compounds, covered with one or more layer(s), of which at least one is an enteric coating layer, whereby the enteric coating layer has mechanical properties such that the compression of the individual units mixed
10 with the tablet excipients into the multiple unit tableted dosage form does not significantly affect the acid resistance of the individually enteric coating layered units.
2. A tableted dosage form according to claim 1, wherein the acid resistance of the
15 individually enteric coating layered units is in coherence with the requirements on enteric coated articles defined in the United States Pharmacopeia.
3. A tableted dosage form according to claim 1, wherein the acid resistance of the individually enteric coating layered units does not decrease more than 10 %
20 during the compression of the individual units into the multiple unit tableted dosage form.
4. A tableted dosage form according to claim 1, wherein the enteric coating layer covering the individual units comprises a plasticized enteric coating layer
25 material.
5. A tableted dosage form according to claim 1, wherein the enteric coating layer covering the individual units has a thickness of at least 10 μm .

6. A tableted dosage form according to claim 1, wherein the individually enteric coating layered units are further covered with an over-coating layer comprising pharmaceutically acceptable excipients.
- 5 7. A tableted dosage form according to claim 1, wherein the active substance is a magnesium salt of omeprazole having a degree of crystallinity which is higher than 70 % as determined by X-ray powder diffraction.
8. A tableted dosage form according to claim 1, wherein the active substance is an
10 alkaline salt of (+)-omeprazole or (-)-omeprazole, preferably a magnesium salt.
9. A tableted dosage form according to claim 1, wherein the dosage form is divisible.
- 15 10. A tableted dosage form according to claim 1, wherein the dosage form is dispersible to a suspension of individually enteric coating layered units in an aqueous liquid.
11. A tableted dosage form according to claim 1, wherein an optionally applied
20 separating layer comprises pharmaceutically acceptable excipients which are soluble, or insoluble but disintegrating in water, and optionally alkaline compounds.
12. A tableted dosage form according to claim 1, wherein the core material is a
25 seed layered with the active substance.
13. A tableted dosage form according to claim 12, wherein the seeds have a size of 0.1 - 2 mm.
- 30 14. A process for the manufacture of a pharmaceutical multiple unit tableted dosage form comprising tablet excipients and individually enteric coating layered

units of a core material containing active substance in the form of omeprazole or one of its single enantiomers or an alkaline salt of omeprazole or one of its single enantiomers, optionally mixed with alkaline compounds, wherein said core material optionally is covered with one or more separating layer(s) and further
5 covered with one or more enteric coating layer(s), whereafter the individually enteric coating layered units are mixed with tablet excipients and compressed into a tablet, and whereby the enteric coating layer has mechanical properties such that the compression of the individual units with the tablet excipients into the multiple unit tableted dosage form does not significantly affect the acid resistance of the
10 individually enteric coating layered units.

15 15. A process according to claim 14, wherein the individually enteric coating layered units are further coated with an over-coating layer before the compression of the individual units into the multiple unit tableted dosage form.

16. A tableted dosage form according to any of claims 1 to 13 for use in therapy.

20 17. A tableted dosage form according to any of claims 1 to 13 for use in inhibiting gastric acid secretion in mammals and man.

18. A tableted dosage form according to any of claims 1 to 13 for use in the treatment of gastrointestinal inflammatory diseases in mammals and man.

25 19. A method for inhibiting gastric acid secretion in mammals and man by administering to a host in need thereof a therapeutically effective dose of a multiple unit tableted dosage form according to any of claims 1 to 13.

30 20. A method for the treatment of gastrointestinal inflammatory diseases in mammals and man by administering to a host in need thereof a therapeutically effective dose of a multiple unit tableted dosage form according to any of claims 1 to 13.

21. A press-through blister package comprising a multiple unit tableted dosage form according to any of claims 1 to 13.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 95/00677

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/26, A61K 9/20, A61K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE, MEDLINE, WPI, WPIL, CLAIMS, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0247983 A2 (AKTIEBOLAGET HÄSSLE), 2 December 1987 (02.12.87), page 5, line 6 - page 9, line 12, examples --	1-18,21
X	EP 0519144 A1 (ILSAN ILAC VE HAMMADELERI SANAYI A.S.), 23 December 1992 (23.12.92) --	1-18,21
A	EP 0365947 A1 (PHARMACIA AB), 2 May 1990 (02.05.90), page 3, line 37 - line 55 -- -----	1-18,21

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search

13 October 1995

Date of mailing of the international search report

21 -10- 1995

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 95/00677

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 19-20
because they relate to subject matter not required to be searched by this Authority, namely:
Methods for treatment of the human or animal body by surgery or therapy,
as well as diagnostic methods (see PCT Rule 39(iv)).
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such
an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/SE 95/00677

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A2- 0247983	02/12/87	SE-T3- 0247983	
		AU-B- 601974	27/09/90
		AU-A- 7191287	05/11/87
		CA-A- 1292693	03/12/91
		DE-A- 3783394	18/02/93
		DK-B- 169988	24/04/95
		EP-A, A, A 0496437	29/07/92
		EP-A, A- 0567201	27/10/93
		ES-T- 2006457	01/01/94
		GB-A- 2189698	04/11/87
		HK-A- 135294	09/12/94
		IE-B- 61416	02/11/94
		JP-C- 1863556	08/08/94
		JP-A- 5294831	09/11/93
		JP-A- 62258320	10/11/87
		NO-B, C- 174239	27/12/93
		SU-A- 1820837	07/06/93
		US-A- 4786505	22/11/88
<hr/>			
EP-A1- 0519144	23/12/92	NONE	
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EP-A1- 0365947	02/05/90	SE-T3- 0365947	
		AU-B- 612525	11/07/91
		AU-A- 4365089	03/05/90
		CA-A- 2000932	26/04/90
		DE-T- 68907177	13/01/94
		ES-T- 2055775	01/09/94
		HK-A- 123394	18/11/94
		JP-A- 2164821	25/06/90
		SE-A- 8803822	26/10/88
		US-A- 5178868	12/01/93
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/26, 9/20, 31/44	A1	(11) International Publication Number: WO 96/01624 (43) International Publication Date: 25 January 1996 (25.01.96)
(21) International Application Number: PCT/SE95/00678 (22) International Filing Date: 7 June 1995 (07.06.95) (30) Priority Data: 9402431-2 8 July 1994 (08.07.94) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): BERGSTRAND, Pontus, John, Arvid [SE/SE]; Walleriusgatan 4, S-412 58 Göteborg (SE). LÖVGREN, Kurt, Ingmar [SE/SE]; Violinvägen 2D, S-435 44 Mölnlycke (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG). Published <i>With international search report.</i>
(54) Title: MULTIPLE UNIT PHARMACEUTICAL PREPARATION CONTAINING PROTON PUMP INHIBITOR (57) Abstract A new pharmaceutical multiple unit tableted dosage form containing as active substance an acid labile H ⁺ K ⁺ -ATPase inhibitor or an alkaline salt thereof or one of its single enantiomers or an alkaline salt thereof, a method for the manufacture of such a formulation, and the use of such a formulation in medicine.		

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Multiple unit pharmaceutical preparation containing proton pump inhibitor.

Field of the invention.

5

The present invention is related to new pharmaceutical preparations in the form of a multiple unit tableted dosage form comprising an active substance in the form of an acid labile H^+K^+ -ATPase inhibitor. The novel tableted dosage form is intended for oral use. Furthermore, the present invention refers to a method for the manufacture of such preparations and, to the use of such preparations in medicine.

10

Background of the invention

15

Acid labile H^+K^+ -ATPase inhibitors also named as gastric proton pump inhibitors are for instance compounds known under the generic names omeprazole, lansoprazole, pantoprazole, pariprazole and leminoprazole.

Compounds of interest for the novel tableted dosage form according to the present invention are compounds of the general formula I or an alkaline salt thereof or one of its single enantiomers or an alkaline salt thereof.

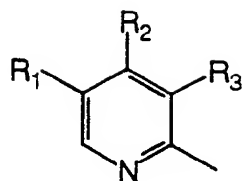
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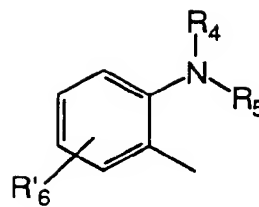
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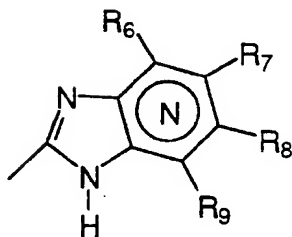
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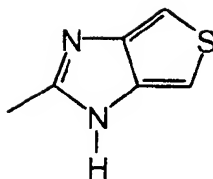
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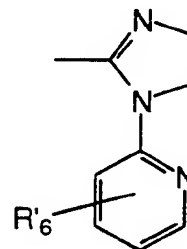
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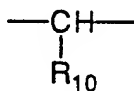


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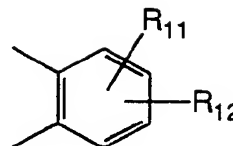


5

X =



or



wherein

- 10 N in the benzimidazole moiety means that one of the carbon atoms substituted by R₆-R₉ optionally may be exchanged for a nitrogen atom without any substituents;

- 15 R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R₄ and R₅ are the same or different and selected from hydrogen, alkyl and aralkyl;

R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

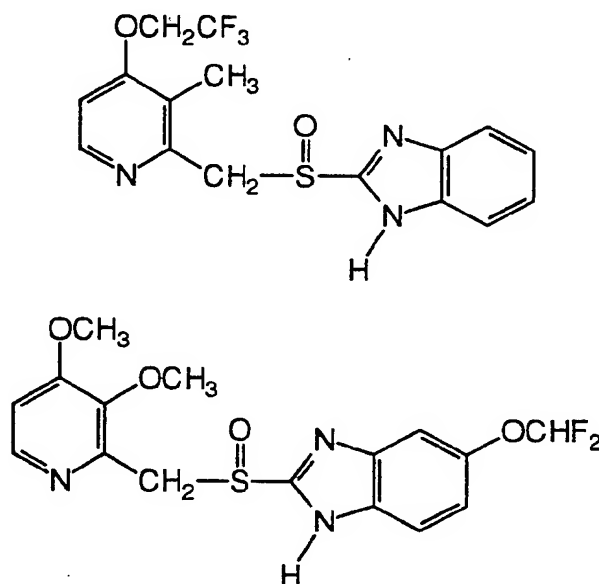
R_6 - R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6 - R_9 form ring structures which may be further substituted;

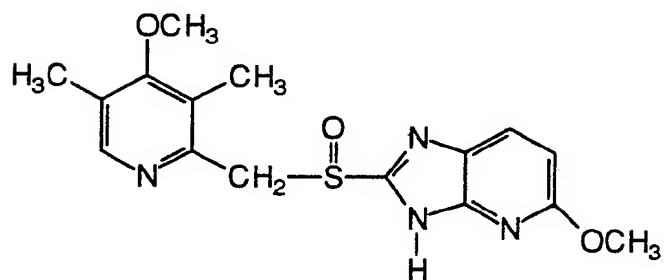
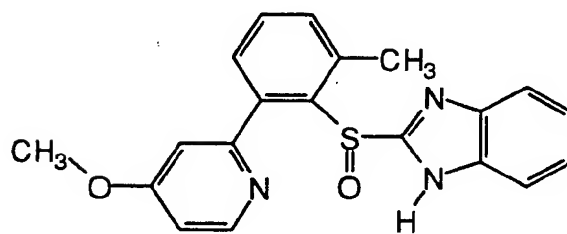
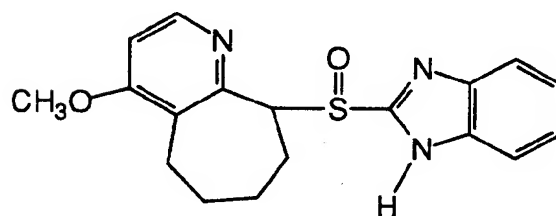
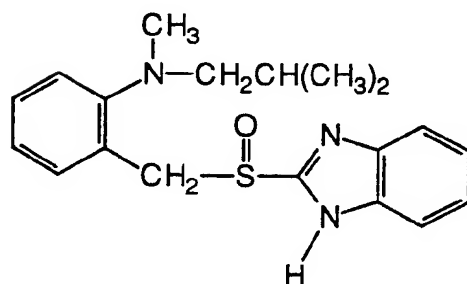
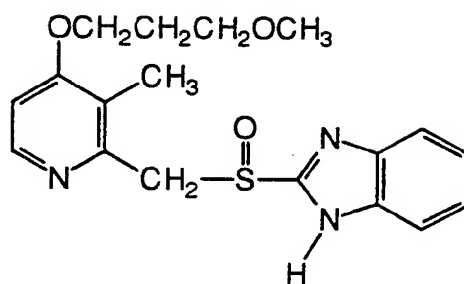
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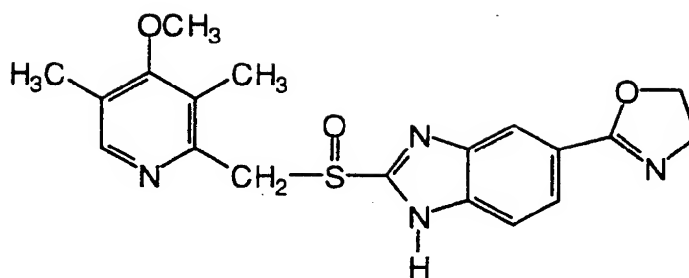
R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl except the compounds 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, 5-fluoro-2-[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and 5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)-methyl]sulfinyl-1H-benzimidazole.

15 Examples of specifically interesting compounds according to formula I are







The active compound used in the tableted dosage form according to the invention may be used in neutral form or in the form of an alkaline salt, such as for instance the Mg^{2+} , Ca^{2+} , Na^{+} or K^{+} salts, preferably the Mg^{2+} salts. The compounds may
5 also be used in the form of one of its single enantiomers or alkaline salts thereof.

Some of the above compounds are for instance disclosed in EP-A1-0005129, EP-A1-174726, EP-A1-166287 and GB 2163747.

10 These active substances are useful for inhibiting gastric acid secretion in mammals and man. In a more general sense, they may be used for prevention and treatment of gastric acid related diseases in mammals and man, including e.g. reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, they may be used for treatment of other gastrointestinal disorders where gastric
15 acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, and in patients with gastrinomas. They may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre-and postoperatively to prevent acid aspiration of gastric acid and to prevent
20 and treat stress ulceration. Further, they may be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections and diseases related to these.

The active compounds are, however, susceptible to degradation/transformation
25 in acidic and neutral media. The degradation is catalyzed by acidic compounds and is stabilized in mixtures with alkaline compounds. The stability of the active

substances is also affected by moisture, heat, organic solvents and to some degree by light.

5 In respect to the stability properties of the active substances, it is obvious that an oral solid dosage form must be protected from contact with the acidic gastric juice and the active substance must be transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid absorption can occur.

10 A pharmaceutical oral dosage form of such acid H^+K^+ -ATPase inhibitors is best protected from contact with acidic gastric juice by an enteric coating layer. In US-A 4,853,230 such an enteric coated preparation is described. Said preparation contains an alkaline core comprising an acidic susceptible substance, a separating layer and an enteric coating layer. In order to further enhance the stability during
15 storage the prepared formulation may optionally be packed with a desiccant.

There is a demand for development of new enteric coating layered multiple unit preparations with good chemical and mechanical stability making it possible to produce well functioning and patient-friendly packages, such as for instance
20 blister packages. Furthermore, there is a demand for formulations having improved patient acceptance, such as divisible and/or dispersible tablets.

A good mechanical stability can be obtained with an enteric coating layered tablet. WO95/01783 describes such a tablet comprising the acid labile compound
25 omeprazole. However, only an enteric coating layered multiple unit tablet can be made divisible and dispersible. A further advantage of a multiple unit dosage form is that it disperses into a multitude of small units in the stomach upon administration.

30 Prior art discloses many different types of multiple unit dosage forms. Usually this type of formulation is requested for controlled release formulations, such as

sustained release formulations. Typically, the multiple unit formulation may be a tablet which disintegrates in the stomach to make available a multitude of coated units, or pellets filled in a capsule. (See for example EP 0 080 341 and US-A 4,853,230).

5

An example to obtain a controlled release dosage form releasing the active substance by diffusion through a membrane is described in US-A 4,927,640, i.e. a multiple-unit system containing small inert cores coated with active substance and a release controlling polymeric membrane. The mechanical properties of such multiple units formulated into tablets are reported in Pharmaceutical Research 10, (1993), p. S-274. Other examples of controlled release dosage forms are for example described in Aulton M.E. (Churchill Livingstone Ed.), Pharmaceutics: The science of dosage form design (1988), p. 316-321.

15 Even if there are examples in the prior art mentioning that pellets may be formulated into tablets there are no examples describing any compositions of such a tablet formulation or a technique to manufacture such a formulation of acid labile H^+K^+ -ATPase inhibitors. In practice, problems arise when enteric coating layered pellets containing acid labile substances are compressed into tablets. If the enteric coating layer does not withstand the compression of the pellets into a tablet the susceptible active substance will be destroyed by penetrating acidic gastric juice, i.e. the acid resistance of the enteric coating layer of the pellets will not be sufficient in the tablet after compression. The above described problems are well illustrated in Reference Examples below.

25

Further, controlled release tablets from enteric coated particles are described in Drugs Made In Germany, 37 No. 2 (1994), p. 53. The teaching in this reference is that a combination of methacrylic acid copolymer (L30D-55) and a copolymer of ethyl acrylate and methyl methacrylate (NE30D) is suitable as coating polymers for enteric coated particles compressed into tablets. Reference Example III shows that this recommendation is not applicable when formulating multiple unit

30

tableted dosage forms of an acidic susceptible substance such as omeprazole. The acid resistance of the pellets compressed into tablets is too low. The cited reference Drugs Made In Germany also states that the use of the copolymer L30D-55 without the addition of the copolymer NE30D as material for enteric coating layer will result in coated pellets which cannot withstand compression forces used during the tableting process. With reference to this statement it is surprisingly found that pellets covered with L30D-55 according to this invention, see Examples, are possible to compress into tablets with fulfilled requirements including acceptable acid resistance of the tablet.

The Applicant is not aware of any working example in the prior art of a multiple unit tableted dosage form comprising an acid labile H^+K^+ -ATPase inhibitor.

15 Description of the invention

The Applicant has now surprisingly found that tablets according to the present invention comprising enteric coating layered units containing an acid labile H^+K^+ -ATPase inhibitor or one of its single enantiomers or an alkaline salt thereof can be manufactured by compressing said units into tablets without significantly affecting the properties of the enteric coating layer. As explained above, if the enteric coating layer is damaged during compression of the enteric coating layered units, the acid resistance of said enteric coating layer in the manufactured tablets will not be sufficient and the manufactured tablets will not fulfill standard requirements on enteric coated articles, such as e.g. those defined in the United States Pharmacopeia (USP), hereby incorporated in a whole by reference. Acid labile H^+K^+ -ATPase inhibitors of interest for the novel dosage form according to the invention are specified in claim 2 and especially preferred compounds are stated in claim 3.

One object of the present invention is to provide a pharmaceutical multiple unit
5 tableted dosage form comprising an acid labile H^+K^+ -ATPase inhibitor or one of
its single enantiomers or an alkaline salt thereof, in which the active substance is
in the form of individually enteric coating layered units compressed into a tablet.
The enteric coating layer(s) covering the individual units of active substance has
properties such that the compression of the units into a tablet does not
10 significantly affect the acid resistance of the individually enteric coating layered
units. The active substance is prevented from degradation and dissolution in
acidic media and has a good stability during long-term storage. The enteric
coating layer covering the individual units disintegrates/dissolves rapidly in near
neutral or alkaline media.

15

Another object of the present invention is to provide a pharmaceutical multiple
unit tableted dosage form comprising an acid labile H^+K^+ -ATPase inhibitor or one
of its single enantiomers or an alkaline salt thereof which is suitable for press-
through blister packages and which also has an improved patient acceptance.

20

A further object of the present invention is to provide a multiple unit tableted
dosage form comprising an acid labile H^+K^+ -ATPase inhibitor or one of its single
enantiomers or an alkaline salt thereof, which is divisible and easy to handle. The
multiple unit tableted dosage form may be dispersed in an aqueous liquid and can
25 be given to patients with swallowing disorders and in pediatrics. Such a
suspension of dispersed enteric coating layered units of appropriate size can be
used for oral administration and also for feeding through a naso-gastric tube.

Detailed description of the invention.

The novel multiple unit tableted dosage form comprising an active substance in the form of an acid labile H^+K^+ ATPase inhibitor or one of its single enantiomers or an alkaline salt thereof is characterized in the following way. Individually enteric coating layered units containing active substance and optionally alkaline substances, are mixed with tablet excipients and compressed into multiple unit tableted dosage forms. With the expression "individual units" is meant small beads, particles, granules or pellets, in the following referred to as pellets.

The compaction process (compression) for formulating the multiple unit tableted dosage form must not significantly affect the acid resistance of the enteric coating layered pellets. In other words the mechanical properties, such as the flexibility and hardness as well as the thickness, of the enteric coating layer(s) must secure that the requirements on enteric coated articles in the United States Pharmacopeia are accomplished and that the acid resistance does not decrease more than 10% during the compression of pellets into tablets.

The flexibility/hardness of enteric coating layers can be characterized for instance as Vickers hardness measured with a Shimadzu micro hardness indentation tester type HMV 2 000.

The acid resistance is defined as the amount of active substance in tablets or pellets after being exposed to simulated gastric fluid, USP, or to 0.1 M HCl(aq) relative to that of unexposed tablets or pellets, respectively. The test is accomplished in the following way. Tablets or pellets are exposed to simulated gastric fluid at a temperature of 37°C. The tablets disintegrate and release the enteric coating layered pellets to the medium. After two hours the pellets are removed and analyzed for content of active substance using High Performance Liquid Chromatography (HPLC). Present values of acid resistance are averages of at least three individual determinations.

Core material

The core material for the individually enteric coating layered pellets can be constituted according to different principles. Seeds layered with active substance,
5 optionally mixed with alkaline compounds, can be used as the core material for the further processing.

The seeds, which are to be layered with the active substance, can be water insoluble seeds comprising different oxides, celluloses, organic polymers and
10 other materials, alone or in mixtures or water soluble seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures. Further, the seeds may comprise active substance in the form of crystals, agglomerats, compacts etc. The size of the seeds is not essential for the present invention and may vary between approximately 0.1 and 2 mm. The seeds layered
15 with active substance are produced either by powder- or solution/suspension layering using for instance granulating or spray coating/layering equipment.

Before the seeds are layered, the active substance may be mixed with further components. Such components can be binders, surfactants, fillers, disintegrating
20 agents, alkaline additives or other pharmaceutically acceptable ingredients, alone or in mixtures. The binders are for example celluloses such as hydroxypropyl methylcellulose, hydroxypropyl cellulose and carboxymethyl-cellulose sodium, polyvinyl pyrrolidone, sugars, starches and other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups
25 of pharmaceutically acceptable non-ionic or ionic surfactants such as for instance sodium lauryl sulfate.

Alternatively, the H^+K^+ -ATPase inhibitor or one of its single enantiomers or an alkaline salt thereof, optionally mixed with alkaline compounds and further
30 mixed with suitable constituents can be formulated into core material. Said core materials may be produced by extrusion/spheronization, balling or compression

utilizing different process equipments. The size of the formulated core materials is approximately between 0.1 and 4 mm and preferably between 0.1 and 2 mm. The manufactured core materials can further be layered with additional ingredients comprising active substance and/or be used for further processing.

5

The active substance is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and a suitable concentration of active substance in the final mixture. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives, can be used.

10

The active substance may also be mixed with an alkaline pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not restricted to, substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

15

20

Alternatively, the aforementioned core material can be prepared by using spray drying or spray congealing technique.

25

The active substance is in the form of an acid labile H^+K^+ -ATPase inhibitor according to formula I or one of its single enantiomers or an alkaline salt thereof. These compounds have an asymmetric centre in the sulfur atom, i.e. exists as two optical isomers (enantiomers). Both the pure enantiomers, racemic mixtures (50%

30

of each enantiomer) and unequal mixtures of the two enantiomers are suitable for the pharmaceutical formulation according to the present invention.

5 Enteric coating layer(s)

Before applying enteric coating layer(s) onto the core material in the form of individual pellets, said pellets may optionally be covered with one or more separating layers comprising pharmaceutical excipients optionally including
10 alkaline compounds such as for instance pH-buffering compounds. This/these separating layer(s) separate(s) the core material from the outer layer(s) being enteric coating layer(s).

The separating layer(s) can be applied to the core material by coating or layering
15 procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating process. As an alternative the separating layer(s) can be applied to the core material by using powder coating technique. The materials for separating layers are pharmaceutically acceptable compounds such as, for instance, sugar,
20 polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methyl-cellulose, ethylcellulose, hydroxypropyl methyl-cellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and
25 other additives may also be included into the separating layer(s).

When the optional separating layer(s) is applied to the core material it may constitute a variable thickness. The maximum thickness of the optional separating layer(s) is normally only limited by processing conditions. The separating layer(s)
30 may serve as a diffusion barrier and may act as a pH-buffering zone. The pH-buffering properties of the separating layer(s) can be further strengthened by

introducing into the layer(s) substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance

- 5 $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$, aluminium hydroxide/sodium bicarbonate coprecipitate or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, carbonic, citric or other suitable, weak, inorganic or organic acids; or
- 10 suitable organic bases, including basic amino acids and salts thereof. Talc or other compounds may be added to increase the thickness of the layer(s) and thereby strengthen the diffusion barrier. The optionally applied separating layer(s) is not essential for the invention. However the separating layer(s) may improve the chemical stability of the active substance and/or the physical properties of the
- 15 novel multiple unit tableted dosage form.

One or more enteric coating layers are applied onto the core material or onto the core material covered with separating layer(s) by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in

20 either water or in suitable organic solvents. As enteric coating layer polymers one or more, separately or in combination, of the following can be used; e.g. solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate,

25 carboxymethylethylcellulose, shellac or other suitable enteric coating layer polymer(s).

The enteric coating layers contain pharmaceutically acceptable plasticizers to obtain the desired mechanical properties, such as flexibility and hardness of the

30 enteric coating layers. Such plasticizers are for instance, but not restricted to,

triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or other plasticizers.

5 The amount of plasticizer is optimized for each enteric coating layer formula, in relation to selected enteric coating layer polymer(s), selected plasticizer(s) and the applied amount of said polymer(s), in such a way that the mechanical properties, i.e. flexibility and hardness of the enteric coating layer(s), for instance exemplified as Vickers hardness, are adjusted so that the acid resistance of the pellets covered with enteric coating layer(s) does not decrease significantly during the
10 compression of pellets into tablets. The amount of plasticizer is usually above 10 % by weight of the enteric coating layer polymer(s), preferably 15 - 50 % and more preferably 20 - 50 %. Additives such as dispersants, colorants, pigments, polymers e.g. poly(ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be included into the enteric coating layer(s). Other compounds may be
15 added to increase film thickness and to decrease diffusion of acidic gastric juices into the acidic susceptible material.

To protect an acidic susceptible substance, such as H^+K^+ -ATPase inhibitors and to obtain an acceptable acid resistance of the multiple unit tableted dosage form
20 according to the invention, the enteric coating layer(s) constitutes a thickness of approximately at least 10 μm , preferably more than 20 μm . The maximum thickness of the applied enteric coating layer(s) is normally only limited by processing conditions.

25

Over-coating layer

Pellets covered with enteric coating layer(s) may further be covered with one or more over-coating layer(s). The over-coating layer(s) can be applied to the enteric
30 coating layered pellets by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using

water and/or organic solvents for the layering process. The materials for over-coating layers are pharmaceutically acceptable compounds such as, for instance sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be included into the over-coating layer(s). Said over-coating layer may further prevent potential agglomeration of enteric coating layered pellets, protect the enteric coating layer towards cracking during the compaction process and enhance the tableting process. The maximum thickness of the applied over-coating layer(s) is normally only limited by processing conditions.

Tablets

The enteric coating layered pellets are mixed with tablet excipients and compressed into a multiple unit tableted dosage form according to the present invention. The enteric coating layered pellets with or without an over-coating layer are mixed with tablet excipients such as fillers, binders, disintegrants, lubricants and other pharmaceutically acceptable additives and compressed into tablets. The compressed tablet is optionally coated with filmforming agent(s) to obtain a smooth surface of the tablet and further enhance the stability of the tablet during packaging and transport. Such a tablet coating layer may further comprise additives like anti-tacking agents, colorants and pigments or other additives to obtain a tablet of good appearance.

The amount of enteric coating layered pellets constitutes less than 75% by weight of the total tablet weight and preferably less than 60 %. By choosing small enteric coating layered pellets in the formulation according to the present invention, the

number of pellets in each tablet can be held high, which in turn makes the tablet divisible with retained dosing accuracy.

5 The mechanical properties, i.e. the flexibility and hardness of the enteric coating layer are essential for the acid resistance of the multiple unit tableted dosage form. The flexibility/hardness of the enteric coating layer surface may be characterized as a preliminary process parameter in the form of Vickers hardness, measured on enteric coating layered pellet(s) before compression of said pellets into tablets. The Vickers hardness may be measured with a Shimadzu micro hardness indentation
10 tester type HMV 2000 (Micro Hardness Testing Machines for Vickers and Knoop Hardness JIS B 7734-1984 and JIS Z 2251-1980). The ability of the enteric coating layer(s) to withstand compression into tablets is, of course, a function of both the amount of applied coating layer and the mechanical properties of said coating layer material. To obtain well functioning enteric coating layered pellets with a
15 reasonable amount of enteric coating layer material by which pellets can be compressed into tablets without significantly affecting the acid resistance, an enteric coating layer surface with a Vickers hardness of less than 8 is preferred. In case the pellets are covered with an over-coating layer the Vickers hardness of the enteric coating layer must be characterized before the over-coating layer is
20 applied. A harder over-coating layer (Vickers hardness higher than 8) can be applied on top of a flexible and softer (Vickers hardness less than 8) enteric coating layer with retained acid resistance during compaction.

Thus, the formulation according to the invention consists of core material
25 containing active substance, optionally mixed with alkaline compound(s), and excipients. The addition of an alkaline material may not be necessary, but such a substance may further enhance the stability of the active substance. The core material is optionally covered with one or more separating layer(s) optionally containing alkaline substance(s). The pellets, optionally covered with a separating
30 layer(s), are then covered with one or more enteric coating layer(s) making the pellets insoluble in acid media, but disintegrating/ dissolving in near neutral to

alkaline media such as, for instance the liquids present in the proximal part of the small intestine, the site where dissolution is wanted. The enteric coating layered pellets may further be covered with an over-coating layer before being formulated into the multiple unit tableted dosage form.

5

Process

The process for the manufacture of the dosage form represents a further aspect of the invention. The pharmaceutical processes can preferably be completely water-based and there are different descriptions given in the accompanying examples below.

15 Use of preparation

The preparation according to the invention is especially advantageous in reducing gastric acid secretion. It is administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general the daily dose will be in the range of 1-1000 mg of active substance.

20

The preparation according to the present invention is also suitable for dispersion in an aqueous liquid with neutral or slightly acidic pH-value before being orally administered or fed through a naso-gastric tube.

- 5 The invention is illustrated more in detail by the following examples.

EXAMPLES

10 Example 1

Core material

	Lansoprazole	400 g
	Sugar sphere seeds	400 g
15	Hydroxypropyl methylcellulose	82 g
	Sodium lauryl sulfate	3 g
	Purified water	1 600 g

Separating layer

20	Core material	400 g
	Hydroxypropyl cellulose	40 g
	Talc	69 g
	Magnesium stearate	6 g
	Purified water	800 g

25

Enteric coating layer

	Pellets covered with separating layer	400 g
	Methacrylic acid copolymer	200 g
	Triethyl citrate	60 g
30	Mono- and diglycerides	10 g
	Polysorbate 80	1 g
	Purified water	420 g

Tablets

Enteric coating layered pellets	82 g
Microcrystalline cellulose	191 g

Suspension layering is performed in a fluid bed apparatus using bottom spray technique. Lansoprazole is sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder. The size of sugar sphere seeds are in the range of 0.25 to 0.35 mm.

The prepared core material is covered with separating layer in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer is sprayed as a water dispersion onto the pellets covered with separating layer in a fluid bed apparatus. Vickers hardness on enteric coating layered pellets is measured to a value of 2.

Enteric coating layered pellets and microcrystalline cellulose are mixed and compressed into tablets using a single punch tableting machine using 10 mm round punches. The upper punch force is set to 5 kN and tablet hardness measured on a Schleuniger hardness tester is 168 - 185 N.

Example 220 Core material

Pantoprazole	600 g
Mannitol	1000 g
Microcrystalline cellulose	300 g
Hydroxypropyl cellulose	100 g
25 Sodium lauryl sulfate	6 g
Purified water	802 g

Separating layer

Core material	400 g
30 Hydroxypropyl methylcellulose	48 g
Purified water	960 g

Enteric coating layer

	Pellets covered with separating layer	200 g
	Methacrylic acid copolymer	100 g
	Triethyl citrate	30 g
5	Mono- and diglycerides	5 g
	Polysorbate 80	0.5 g
	Purified water	309 g

Tablets

10	Enteric coating layered pellets	200 g
	Microcrystalline cellulose	299 g
	Sodium stearyl fumarate	1.2 g

Sodium lauryl sulfate is dissolved in purified water to form the granulation liquid.

- 15 Pantoprazole, mannitol, microcrystalline cellulose and hydroxypropyl cellulose are dry-mixed. The granulation liquid is added to the powder mixture and the mass is wet-mixed.

The wet mass is forced through an extruder equipped with screens, aperture size 0.5 mm.

- 20 The extrudate is spheronized on a friction plate in a spheronizing apparatus. The core material is dried in a fluid bed dryer and classified. The prepared core material is covered with separating layer in a fluid bed apparatus with a hydroxypropyl methyl-cellulose/water solution.

- 25 The enteric coating layer is applied to the pellets covered with separating layer from an aqueous dispersion of methacrylic acid copolymer plasticized with triethyl citrate to which a mono- and diglycerides/polysorbate dispersion has been added. The pellets are dried in a fluid bed apparatus.

- 30 Enteric coating layered pellets, microcrystalline cellulose and sodium stearyl fumarate are mixed and compressed into tablets with a tablet weight corresponding to 20 mg active substance, using a single punch tableting machine equipped with 10 mm round punches.

Example 3Core material

	Pantoprazole	500 g
5	Sugar sphere seeds	500 g
	Hydroxypropyl methylcellulose	150 g
	Colloidal silicon dioxide	3 g
	Purified water	1 400 g

10 Separating layer

	Core material	500 g
	Hydroxypropyl cellulose	40 g
	Talc	67 g
	Magnesium stearate	6 g
15	Purified water	800 g

Enteric coating layer

	Pellets covered with separating layer	500 g
	Methacrylic acid copolymer	200 g
20	Triethyl citrate	60 g
	Purified water	392 g

Tablets

	Enteric coating layered pellets	430 g
25	Microcrystalline cellulose	871 g
	Sodium stearyl fumarate	3 g

30 Pantoprazole, part of the hydroxypropyl methylcellulose and colloidal silicon dioxide are dry-mixed forming a powder mixture. Sugar sphere seeds (0.25-0.35 mm) are layered with the powder in a centrifugal fluidized coating granulator while spraying a hydroxypropyl methylcellulose solution (6 %, w/w).

The prepared core material is dried and covered with separating layer in a centrifugal fluidized coating granulator. A fluid bed apparatus is used for enteric coating layering.

Enteric coating layered pellets and tablet excipients are mixed and compressed into tablets using a rotary tableting machine equipped with 6 pairs of 10 mm round punches. The amount of active substance is approx. 20 mg.

5 Example 4

Core material

	Leminoprazole	200 g
	Silicon dioxide seeds	200 g
10	Hydroxypropyl methylcellulose	35 g
	Sodium lauryl sulfate	2 g
	Purified water	700 g

Separating layer

15	Core material	400 g
	Hydroxypropyl methylcellulose	32 g
	Purified water	700 g

Enteric coating layer

20	Pellets covered with separating layer	400 g
	Methacrylic acid copolymer	250 g
	Polyethylene glycol 400	50 g
	Mono- and diglycerides	10 g
	Polysorbate 80	1 g
25	Purified water	650 g

Tablets

	Enteric coating layered pellets	500 g
	Microcrystalline cellulose	1496 g
30	Sodium stearyl fumarate	2 g

Suspension layering is performed in a fluid bed apparatus. Leminoprazole is sprayed onto the seeds of silicon dioxide (size range 0.15 - 0.3 mm) from a water suspension containing the dissolved binder and a surface active ingredient.

35

The prepared core material is covered with separating layer in a fluid bed apparatus using a hydroxypropyl methylcellulose solution. The enteric coating layer material is

sprayed as a water dispersion onto pellets in a fluid bed apparatus. Enteric coating layered pellets and the tableting excipients are mixed and compressed into tablets as described in Example 2.

5 Example 5

Enteric coating layer

Pellets covered with separating layer (manufacturing and composition as in Example 1)

		500 g
10	Methacrylic acid copolymer	250 g
	Polyethylene glycol 6000	75 g
	Mono- and diglycerides	12.5 g
	Polysorbate 80	1.2 g
	Purified water	490 g

15

Tablets

	Enteric coating layered pellets	600 g
	Microcrystalline cellulose	1 395 g
	Sodium stearyl fumarate	5 g

20

Enteric coating layered pellets, microcrystalline cellulose and sodium stearyl fumarate are mixed and compressed into tablets as described in Example 3.

Example 6

25

Enteric coating layer

Pellets covered with separating layer (manufacturing and composition as in Example 1)

		400 g
	Hydroxypropyl methylcellulose phthalate	400 g
30	Diethyl phthalate	80 g
	Ethanol	1 600 g
	Acetone	4 000 g

Tablets

35	Enteric coating layered pellets	500 g
	Microcrystalline cellulose	1 500 g
	Magnesium stearate	5 g

Enteric coating layering is performed by spraying a solution in a fluid bed. Enteric coating layered pellets, microcrystalline cellulose and magnesium stearate are mixed and compressed into tablets as described in Example 3.

5

Example 7Core material

	Lansoprazole	400 g
10	Sugar sphere seeds (non-pareils)	400 g
	Hydroxypropyl methylcellulose	80 g
	Purified water	1 600 g

Separating layer

15	Core material	800 g
	Hydroxypropyl cellulose	80 g
	Talc	137 g
	Magnesium stearate	11 g
	Purified water	1 600 g

20

Enteric coating layer

	Pellets covered with separating layer	800 g
	Methacrylic acid copolymer	400 g
	Triethyl citrate	120 g
25	Mono- and diglycerides	8 g
	Polysorbate 80	1 g
	Purified water	800 g

Tablets

30	Enteric coating layered pellets	1 000 g
	Dibasic calcium phosphate anhydrous	1 760 g
	Microcrystalline cellulose	440 g
	Magnesium stearate	16 g

35 Suspension layering is performed in a fluid bed apparatus. Lansoprazole is sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder.

The prepared core material is covered with separating layer in a fluid bed with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer is sprayed as a dispersion onto the pellets covered with separating layer in a fluid bed.

- 5 Enteric coating layered pellets, dibasic calcium phosphate anhydrous in granulated form, microcrystalline cellulose and magnesium stearate are mixed and compressed into tablets as described in Example 3. Upper punch force is set to approx 30 kN.

Example 8

10

Tablets

Enteric coating layered pellets (manufacturing and composition as in Example 1)

1.00 kg

Microcrystalline cellulose

1.45 kg

- 15 Anhydrous lactose

0.14 kg

Starch

0.23 kg

Povidone

0.18 kg

Purified water

0.836 kg

- 20 Povidone is dissolved in water. Microcrystalline cellulose, anhydrous lactose and starch are dry-mixed. The povidone solution is added while wet-mixing. The wet mass is dried in an oven. The granulated mass is milled using an oscillating granulator.

- 25 Enteric coating layered pellets and the prepared granulate are mixed and compressed into engraved and scored tablets using a rotary tableting machine equipped with 16 pairs of oval, 8.5x17 mm, tablet punches.

Example 9

- 30 Over-coating layer

Enteric coating layered pellets (manufacturing and composition as in Example 7)

400 g

Hydroxypropyl methylcellulose

120 g

Purified water

2 280 g

35

Tablets

Over-coating layered pellets	100 g
Microcrystalline cellulose	233 g

- 5 In a fluid bed apparatus a hydroxypropyl methylcellulose solution is sprayed onto enteric coating layered pellets. The Vickers hardness on the enteric coating layered pellets before applying the over-coating layer is 2 and Vickers hardness measured on the over-coating layered pellets is 11. Pellets covered with over-coating layer are mixed with microcrystalline cellulose and compressed into tablets as in Example 2.

10

Example 10Core material

Pantoprazole	100 g
15 Sugar sphere seeds	200 g
Hydroxypropyl cellulose	25 g
Purified water	607 g

Separating layer

20 Core material	200 g
Hydroxypropyl cellulose	20 g
Talc	34 g
Magnesium stearate	3 g
Purified water	400 g

25

Enteric coating layer

Pellets covered with separating layer	200 g
Methacrylic acid copolymer	100 g
Triethyl citrate	30 g
30 Mono- and diglycerides	5 g
Polysorbate 80	0.5 g
Purified water	282 g

Tablets

Enteric coating layered pellets	100 g
Microcrystalline cellulose	232 g

Sodium stearyl fumarate 1 g

Suspension layering is performed in a fluid bed apparatus. Pantoprazole is sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder.

- 5 The prepared core material is covered with separating layer in a fluid bed apparatus. The enteric coating layer is sprayed as a water dispersion onto the pellets covered with separating layer in a fluid bed apparatus.

- 10 Enteric coating layered pellets and tablet excipients are mixed and compressed into tablets weighing approx 600 mg using a single punch tableting machine using 12 mm round punches. The upper punch force is set to 5 kN and tablet hardness measured on a Schleuniger hardness tester is 200 - 220 N.

Example 11

15

Enteric coating layer

Core material (no separating layer)	500 g
Methacrylic acid copolymer	500 g
Triethyl citrate	150 g
20 Mono- and diglycerides	25 g
Polysorbate 80	2.5 g
Purified water	978 g

Tablets

25

Enteric coating layered pellets	800 g
Microcrystalline cellulose	1 860 g
Sodium stearyl fumarate	7 g

- 30 Core materials are produced as in Example 1 and in Example 10. Enteric coating layered pellets and tablet excipients are compressed as described in Example 3.

Example 12Core material

	Pariprazole	100 g
5	Sugar sphere seeds	200 g
	Povidone	25 g
	Purified water	750 g

Separating layer

10	Core material	100 g
	Povidone	5 g
	Purified water	150 g

Enteric coating layer

15	Pellets covered with separating layer	100 g
	Methacrylic acid copolymer	50 g
	Triethyl citrate	15 g
	Talc	15 g
	Purified water	125 g

20

Tablets

	Enteric coating layered pellets	125 g
	Microcrystalline cellulose	300 g

Suspension layering is performed in a fluid bed apparatus. Pariprazole is sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder.

25 The prepared core material is covered with separating layer in a fluid bed apparatus. The enteric coating layer is sprayed as a water dispersion onto the pellets covered with separating layer in a fluid bed apparatus.

Enteric coating layered pellets and microcrystalline cellulose are mixed and compressed into tablets as described in Example 1.

Example 13Enteric coating layer

	Pellets covered with separating layer	200 g
5	Hydroxypropyl methylcellulose acetate succinate	100 g
	Triethyl citrate	30 g
	Purified water	309 g
	Ethanol	720 g

10 Tablets

	Enteric coating layered pellets	100 g
	Microcrystalline cellulose	227 g
	Crospovidone	5 g
	Sodium stearyl fumarate	1 g

The pellets covered with separating layer are produced as in Example 7.

The enteric coating layer is applied in a fluid bed from a water/ethanol solution.

The Vickers hardness on enteric coating layered pellets is measured to a value of 5. Enteric coating layered pellets and tablet excipients are mixed and compressed

15 into tablets as in Example 2.

Example 14Enteric coating layer

20	Pellets covered with separating layer	200 g
	Methacrylic acid copolymer	200 g
	Triethyl citrate	60 g
	Mono- and diglycerides	10 g
	Polysorbate 80	1 g
25	Purified water	391 g

Over-coating layer

	Enteric coating layered pellets	471 g
	Hydroxypropyl methylcellulose	6 g
30	Magnesium stearate	0.2 g
	Purified water	120 g

Tablets

Over-coating layered pellets	140 g
Microcrystalline cellulose	114 g
Sodium stearyl fumarate	0.4 g

5

Pellets covered with separating layer are produced according to Example 7.

The enteric coating layer and the over-coating layer are sprayed onto pellets in a fluid bed apparatus. Over-coating layered pellets and tablet excipients are compressed using a single punch (round, 12 mm) tableting machine. Upper punch

10 force is set to 6 kN.

Example 15Enteric coating layer

15 Pellets covered with separating layer	200 g
Methacrylic acid copolymer	40 g
Triethyl citrate	12 g
Mono- and diglycerides	2 g
Polysorbate 80	0.2 g
20 Purified water	78 g

Over-coating layer

Enteric coating layered pellets	200 g
Hydroxypropyl methylcellulose	4 g
25 Magnesium stearate	0.1 g

Tablets

Over-coating layered pellets	69 g
Microcrystalline cellulose	230 g
30 Sodium stearyl fumarate	0.7 g

Pellets covered with separating layer are produced according to Example 7.

The enteric coating layer and the over-coating layer are sprayed onto pellets in a fluid bed apparatus. The amount of enteric coating layer material used in this
 35 example corresponds to an enteric coating layer thickness of approx. 20 μ m. Over-coating layered pellets and tablet excipients are compressed using a single punch (round, 10 mm) tableting machine. Tablet weight approx. 330 mg.

Example 16Enteric coating layer

	Pellets covered with separating layer	500 g
5	Cellulose acetate phtalate	375 g
	Diethyl phthalate	150 g
	Acetone	2 000 g
	Ethanol	2 000 g

10 Tablets

	Enteric coating layered pellets	100 g
	Microcrystalline cellulose	300 g
	Crospovidone	8 g
	Sodium stearyl fumarate	1 g

The pellets covered with separating layer are produced as in Example 7.

The enteric coating layer is applied in a fluid bed from a acetone/ethanol solution.

Enteric coating layered pellets and tablet excipients are mixed and compressed into tablets as in Example 2.

15

The results from tests on acid resistance of the enteric coating layered pellets and the compressed tablets are disclosed in Table I, below.

Table I

20

Example No	Acid resistance, pellets (%)	Acid resistance, tablets (%)
1	100	93
10	99	93

Comments:

25 Surprisingly, the acid resistance, tablets, shows that the enteric coating layer according to the present invention sufficiently withstands compression.

Reference example ITablets

	Omeprazole enteric coating layered pellets	180 g
5	Microcrystalline cellulose	219 g
	Sodium stearyl fumarate	1 g

Omeprazole pellets from Losec® 40 mg capsules are mixed with microcrystalline cellulose and sodium stearyl fumarate and compressed into tablets using a single punch tableting machine. The Vickers hardness on the enteric coating layered pellets is measured to a value of 22. The tablet tooling is round with a diameter of 10 mm. Punch force is set to 3.7 kN.

Reference example II

15

Tablets

	Lansoprazole enteric coating layered pellets (content of Lanzo® 30 mg capsules)	276 g
20	Microcrystalline cellulose	644 g

Lansoprazole pellets are mixed with microcrystalline cellulose and tableted in a single punch tableting machine. The Vickers hardness on enteric coating layered pellets is measured to a value of 18. The tablet tooling is round with a diameter of 12 mm. Punch force is set to 3.6 kN.

25

Reference example IIICore material

	Magnesium omeprazole	15.0 kg
30	Sugar sphere seeds	15.0 kg
	Hydroxypropyl methylcellulose	2.25 kg
	Purified water	40 kg

Separating layer

	Core material	15.0 kg
	Hydroxypropyl cellulose	1.5 kg
	Talc	2.57 kg
5	Magnesium stearate	0.21 kg
	Purified water	30 kg

Enteric coating layer

- 10 Pellets covered with separating layer 200 g
- 10 Enteric coating layer material is used as described in Drugs Made In Germany 37, No. 2 (1994), p.53, Table 1, Formulation no. 9.
- The amount of coating polymer as calculated in above reference is 40 % (w/w).

15 Over-coating layer

	Enteric coating layered pellets	291 g
	Hydroxypropyl methylcellulose	4 g
	Magnesium stearate	0.2 g
	Purified water	80 g

20

Tablets

	Over-coating layered pellets	75 g
	Microcrystalline cellulose	174 g
	Sodium stearyl fumarate	0.6 g

25

- Suspension layering is performed in a fluid bed apparatus. Omeprazol magnesium is sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder. The separating layer, enteric coating layer and the over-coating layer are sprayed onto pellets in a fluid bed apparatus. The over-coating layer is applied to prevent sticking of pellets before tableting. Over-coating layered pellets and tablet excipients are tableted as in Example 1. Upper punch force is set to 5 kN.

30

- The results from tests on acid resistance of the enteric coating layered pellets and the compressed tablets are disclosed in Table II, below.

35

Table II

Reference example number	Acid resistance pellets (%),	Acid resistance tablets (%),
I	97	6
II	98	25
III	98	82

Comments:

5

As can be seen from the presented data, the enteric coating layer of the products studied, including the two marketed products (Reference examples I and II) do not possess the mechanical properties required to withstand compression into tablets.

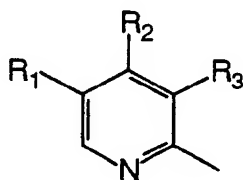
CLAIMS

1. An oral pharmaceutical multiple unit tableted dosage form comprising tablet excipients and individually enteric coating layered units of a core material
- 5 containing active substance in the form of an acid labile H^+K^+ -ATPase inhibitor or one of its single enantiomers or an alkaline salt thereof, optionally mixed with alkaline compounds, covered with one or more layer(s) of which at least one is an enteric coating layer, whereby the enteric coating layer has mechanical properties such that the compression of the individual units mixed with the tablet excipients
- 10 into the multiple unit tableted dosage form does not significantly affect the acid resistance of the individually enteric coating layered units.
2. A tableted dosage form according to claim 1, wherein the active substance is a compound of the general formula I or an alkaline salt thereof or one of its single
- 15 enantiomers or an alkaline salt thereof

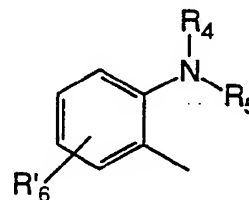


wherein

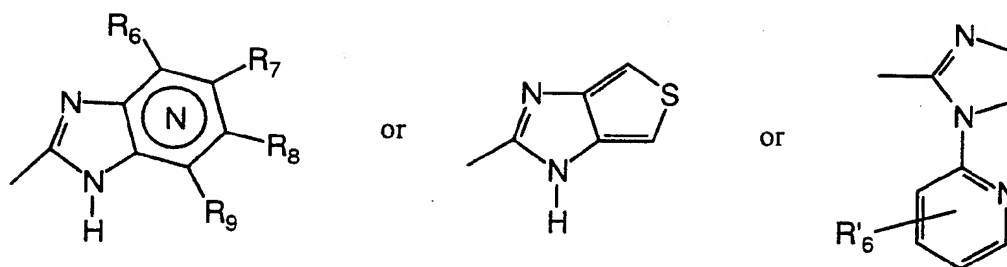
20 Het₁ is



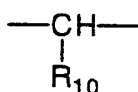
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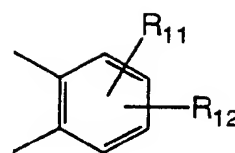
Het₂ is



X =



or



5 wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R_6 - R_9 , optionally may be exchanged for a nitrogen atom without any substituents;
 10 R_1 , R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

15

R'_6 is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R_6 - R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxy carbonyl, oxazolyl, trifluoroalkyl, or

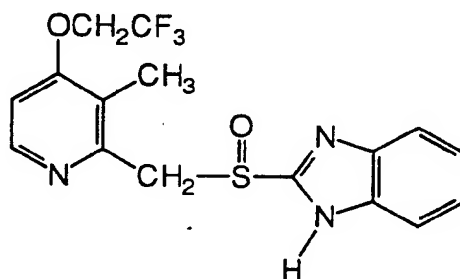
20 adjacent groups R_6 - R_9 form ring structures which may be further substituted;

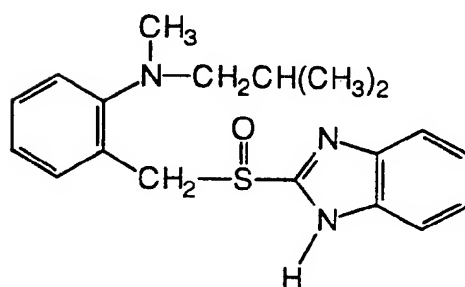
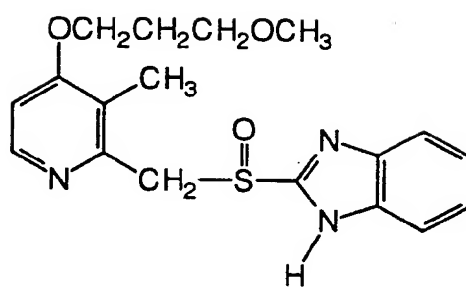
R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl except the compounds 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-

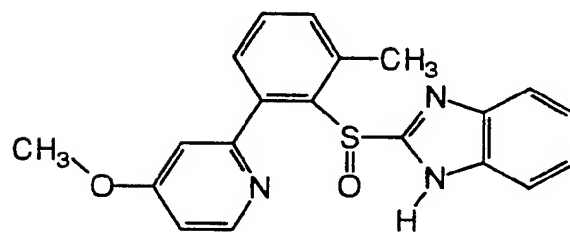
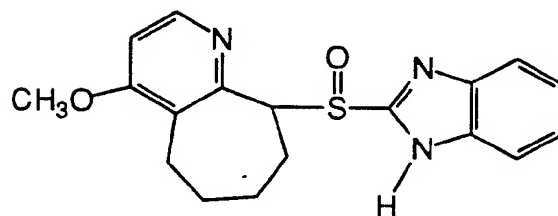
- 5 pyridinyl)methyl]sulfinyl]-1H-benzimidazole, 5-fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and 5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or their single enantiomers or alkaline salts thereof.

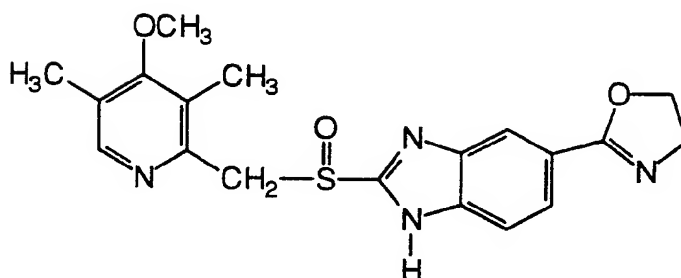
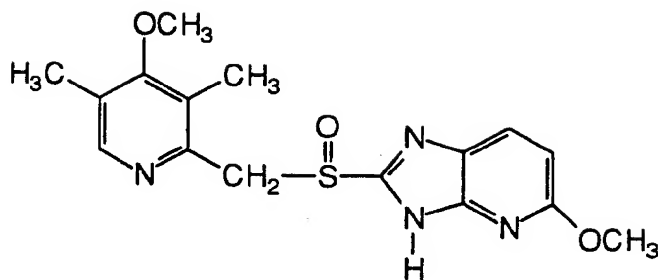
- 10 3. A tableted dosage form according to claim 1, wherein the active substance is one of the following compounds





5





5

or an alkaline salt thereof or one of its single enantiomers or an alkaline salt thereof.

4. A tableted dosage form according to claim 1, wherein the acid resistance of the individually enteric coating layered units is in coherence with the requirements on enteric coated articles defined in the United States Pharmacopeia.

5. A tableted dosage form according to claim 1, wherein the acid resistance of the individually enteric coating layered units does not decrease more than 10 % during the compression of the individually enteric coating layered units into the multiple unit tableted dosage form.

6. A dosage form according to claim 1, wherein the enteric coating layer covering the individual units comprises a plasticized enteric coating layer material.

8. A tableted dosage form according to claim 1, wherein the individually enteric coating layered units are further covered with an over-coating layer comprising pharmaceutically acceptable excipients.
- 5 9. A tableted dosage form according to claim 1, wherein the dosage form is divisible.
- 10 10. A tableted dosage form according to claim 1, wherein the dosage form is dispersible to a suspension of individually enteric coating layered units in an aqueous liquid.
- 15 11. A tableted dosage form according to claim 1, wherein an optionally applied separating layer comprises pharmaceutically acceptable excipients which are soluble, or insoluble but disintegrating in water, and optionally alkaline compounds.
- 20 12. A tableted dosage form according to claim 1, wherein the core material is a seed layered with the active substance.
- 25 13. A tableted dosage form according to claim 12, wherein the seeds have a size of 0.1 - 2 mm.
- 30 14. A process for the manufacture of a pharmaceutical multiple unit tableted dosage form comprising tablet excipients and individually enteric coating layered units of a core material containing active substance as defined in claim 1 optionally mixed with alkaline compounds, wherein the core material is optionally covered with one or more separating layer(s) and further covered with one or more enteric coating layer(s), whereafter the individually enteric coating layered units are compressed into a tablet and whereby the enteric coating layer has mechanical properties such that the compression of the individual units mixed with the tablet excipients into the multiple unit tableted dosage form does not

significantly affect the acid resistance of the individually enteric coating layered units.

15. A process according to claim 14, wherein the individually enteric coating
5 layered units are further coated with an over-coating layer before compression of the individual units into the multiple unit tableted dosage form.
16. A tableted dosage form according to any of claims 1 to 13 for use in therapy.
- 10 17. A tableted dosage form according to any of claims 1 to 13 for use in inhibiting gastric acid secretion in mammals and man.
18. A tableted dosage form according to any of claims 1 to 13 for use in the treatment of gastrointestinal inflammatory diseases in mammals and man.
15
19. A method for inhibiting gastric acid secretion in mammals and man by administering to a host in need thereof a therapeutically effective dose of a multiple unit tableted dosage form according to any of claims 1 to 13.
- 20 20. A method for the treatment of gastrointestinal inflammatory diseases in mammals and man by administering to a host in need thereof a therapeutically effective dose of a multiple unit tableted dosage form according to any of claims 1 to 13.
- 25 21. A press-through blister package comprising a multiple unit tableted dosage form according to any of claims 1 to 13.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 95/00678

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/26, A61K 9/20, A61K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE, MEDLINE, WPI, WPIL, CLAIMS, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0247983 A2 (AKTIEBOLAGET HÄSSLE), 2 December 1987 (02.12.87), page 5, line 6 - page 9, line 12, examples --	1-18,21
X	EP 0519144 A1 (ILSAN ILAC VE HAMMADELERI SANAYI A.S.), 23 December 1992 (23.12.92) --	1-18,21
A	EP 0365947 A1 (PHARMACIA AB), 2 May 1990 (02.05.90), page 3, line 37 - line 55 --	1-18,21
A	WO 9222284 A1 (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH), 23 December 1992 (23.12.92) -- -----	1-18,21

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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"&" document member of the same patent family

Date of the actual completion of the international search

13 October 1995

Date of mailing of the international search report

21.10.95

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 95/00678

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 19-20
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/SE 95/00678

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A2- 0247983	02/12/87	SE-T3- 0247983 AU-B- 601974 AU-A- 7191287 CA-A- 1292693 DE-A- 3783394 DK-B- 169988 EP-A, A, A 0496437 EP-A, A- 0567201 ES-T- 2006457 GB-A- 2189698 HK-A- 135294 IE-B- 61416 JP-C- 1863556 JP-A- 5294831 JP-A- 62258320 NO-B, C- 174239 SU-A- 1820837 US-A- 4786505	27/09/90 05/11/87 03/12/91 18/02/93 24/04/95 29/07/92 27/10/93 01/01/94 04/11/87 09/12/94 02/11/94 08/08/94 09/11/93 10/11/87 27/12/93 07/06/93 22/11/88
EP-A1- 0519144	23/12/92	NONE	
EP-A1- 0365947	02/05/90	SE-T3- 0365947 AU-B- 612525 AU-A- 4365089 CA-A- 2000932 DE-T- 68907177 ES-T- 2055775 HK-A- 123394 JP-A- 2164821 SE-A- 8803822 US-A- 5178868	11/07/91 03/05/90 26/04/90 13/01/94 01/09/94 18/11/94 25/06/90 26/10/88 12/01/93
WO-A1- 9222284	23/12/92	AU-A- 1974692 BG-A- 98286 CN-A- 1067809 CZ-A- 9302764 DE-A- 4219390 EP-A- 0519365 EP-A- 0589981 FI-D- 935677 JP-T- 6508118 NO-A, D- 934648	12/01/93 15/08/94 13/01/93 13/07/94 24/12/92 23/12/92 06/04/94 00/00/00 14/09/94 16/12/93



(51) International Patent Classification ⁶ : A61K 9/26, 9/20, 31/44	A1	(11) International Publication Number: WO 96/01625
		(43) International Publication Date: 25 January 1996 (25.01.96)

(21) International Application Number: PCT/SE95/00680

(22) International Filing Date: 7 June 1995 (07.06.95)

(30) Priority Data:
9402431-2 8 July 1994 (08.07.94) SE

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(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH,
CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE,
KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN,
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TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT,
BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN,
ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD,
SZ, UG).

Published
With international search report.

(54) Title: MULTIPLE UNIT TABLETED DOSAGE FORM CONTAINING PROTON PUMP INHIBITOR

(57) Abstract

A new pharmaceutical multiple unit tableted dosage form containing an acid labile, pharmaceutically active substance with gastric inhibitory effect, or one of its single enantiomers or an alkaline salt thereof, a method for the manufacture of such a formulation, and the use of such a formulation in medicine.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: A61K 9/26, 9/20, 31/44	A1	(11) International Publication Number: WO 96/01625 (43) International Publication Date: 25 January 1996 (25.01.96)
(21) International Application Number: PCT/SE95/00680 (22) International Filing Date: 7 July 1995 (07.07.95) (30) Priority Data: 9402431-2 8 July 1994 (08.07.94) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): BERGSTRAND, Pontus, John, Arvid [SE/SE]; Walleriusgatan 4, S-412 58 Göteborg (SE). LÖVGREN, Kurt, Ingmar [SE/SE]; Violinvägen 2D, S-435 44 Mölnlycke (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG). Published <i>With international search report.</i>
(54) Title: MULTIPLE UNIT TABLETED DOSAGE FORM CONTAINING PROTON PUMP INHIBITOR (57) Abstract A new pharmaceutical multiple unit tableted dosage form containing an acid labile, pharmaceutically active substance with gastric inhibitory effect, or one of its single enantiomers or an alkaline salt thereof, a method for the manufacture of such a formulation, and the use of such a formulation in medicine.		

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Multiple unit tableted dosage form containing
proton pump inhibitor.

Field of the invention

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The present invention is related to new pharmaceutical preparations in the form of a multiple unit tableted dosage form comprising acid labile heterocyclic compounds or one of its single enantiomers or alkaline salts thereof with gastric acid inhibitory effect. The novel tableted dosage form is intended for oral use.

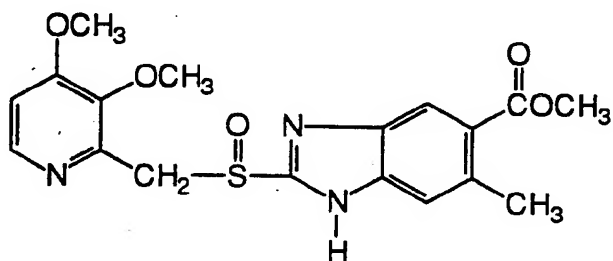
10 Furthermore, the present invention refers to a method for the manufacture of such preparations and, to the use of such preparations in medicine.

Background of the invention

15

Acid labile heterocyclic compounds with gastric inhibitory effect are for instance compounds described in EP-A1-0005129, WO 90/06925 and WO 91/19712. The following compounds I and II are of specific interest for the novel tableted dosage form according to the present invention

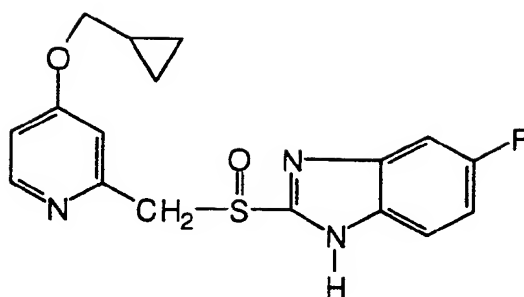
20



I

5-Carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole and

25



II

5-Fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

5

Compounds I and II used in the compositions of the invention may be used in neutral form or in the form of an alkaline salt, such as for instance the Mg^{2+} , Ca^{2+} , Na^{2+} or K^{+} salts, preferably Mg^{2+} salts. These compounds may be used in racemic form or in the form of one of its single enantiomers. The latter are described in

10 PCT/SE 94/00510 and PCT/SE 94/00511 both filed on May 27, 1994.

These active substances are, as already mentioned, useful for inhibiting gastric acid secretion in mammals and man. In a more general sense, they may be used for prevention and treatment of gastric acid related diseases in mammals and

15 man, including e.g. reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, they may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, and in patients with

20 gastrinomas. They may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre-and postoperatively to prevent acid aspiration of gastric acid and to prevent and treat stress ulceration. Further, they may be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections and diseases related to these.

25

These compounds with gastric inhibitory effect are, however, susceptible to degradation/transformation in acidic and neutral media. The degradation is catalyzed by acidic compounds and they are usually stabilized in mixtures with alkaline compounds. The stability of the compounds is also affected by moisture,
5 heat, organic solvents and to some degree by light.

In respect to the stability properties of these acidic susceptible compounds, it is obvious that the active compound in an oral solid dosage form must be protected from contact with the acidic gastric juice and must be transferred in intact form to
10 that part of the gastrointestinal tract where pH is near neutral and where rapid absorption of the pharmaceutically active substance can occur.

A pharmaceutical oral dosage form of the specific active compound is best protected from contact with acidic gastric juice by an enteric coating layer. In US-
15 A 4,853,230 enteric coated preparations of acid labile substances are described. Said preparations contain an alkaline core comprising the active substance, a separating layer and an enteric coating layer. In order to further enhance the stability during storage the prepared formulation may optionally be packed with a desiccant.

20 There has been a demand for development of new enteric coating layered multiple unit preparations with good chemical and mechanical stability making it possible to produce well functioning and patient-friendly packages, such as for instance blister package. Furthermore, there is a demand for formulations having
25 an improved patient acceptance, such as divisible and/or dispersible tablets.

A good mechanical stability can be obtained with an enteric coating layered tablet (WO 95/01783 describes such a tablet comprising the acid labile compound, omeprazole). However, only an enteric coating layered multiple unit tablet can be
30 made divisible and dispersible. A further advantage of a multiple unit dosage

form is that it disperses into a multitude of small units in the stomach upon administration.

5 Prior art discloses many different types of multiple unit dosage forms. Usually this type of formulation is requested for controlled release formulations, such as sustained release formulations. Typically, the multiple unit formulation may be a tablet which disintegrates in the stomach to make available a multitude of coated units, or pellets filled in a capsule. (See for example EP 0 080 341 and US-A 4,853,230).

10

An example to obtain a controlled release dosage form releasing the active substance by diffusion through a membrane is described in US-A 4,927,640, i.e. a multiple-unit system containing small inert cores coated with active substance and a release controlling polymeric membrane. The mechanical properties of such multiple units formulated into tablets are reported in Pharmaceutical Research, 10 (1993), p. S-274. Other examples of controlled release dosage forms are for example described in Aulton M.E. (Churchill Livingstone), *Pharmaceutics: The science of dosage form design* (1988), p. 316-321.

20 Even if there are examples in the prior art mentioning that pellets may be formulated into tablets, there are no examples describing any compositions of such a tablet formulation or a technique to manufacture such a formulation comprising an acid labile substance. In practice, problems arise when enteric coating layered pellets, especially containing acidic susceptible substances are compressed into tablets. If the enteric coating layer does not withstand the compression of the pellets into a tablet the susceptible active substance will be destroyed by penetrating acidic gastric juice, i.e. the acid resistance of the enteric coating layer of the pellets will not be sufficient in the tablet after compression. The above described problems are well illustrated in Reference Examples below.

30

Further, controlled release tablets from enteric coated particles are described in Drugs Made In Germany, 37 No. 2 (1994), p. 53. The teaching in this reference is that a combination of a methacrylic acid copolymer (L30D-55) and a copolymer of ethyl acrylate and methyl methacrylate (NE30D) is suitable as coating polymers for enteric coated particles compressed into tablets. Reference Example III shows that this recommendation is not applicable when formulating multiple unit tableted dosage forms of acidic susceptible substances. The acid resistance of the pellets compressed into a tablet is too low. The cited reference Drugs Made In Germany also states that the use of the copolymer L30D-55 without the addition of the copolymer NE30D as material for enteric coating layers will result in coated pellets which cannot withstand compression forces used during the tableting process. With reference to this statement it is surprisingly found that pellets covered with L30D-55 according to this invention, see Examples below, are possible to compress into tablets with fulfilled requirements including acceptable acid resistance of the tablet.

The Applicant is not aware of any working example in the prior art of a multiple unit tableted dosage form comprising an acid labile heterocyclic compound.

Description of the invention

The Applicant has now surprisingly found that tablets according to the present invention comprising enteric coating layered units containing an acid labile heterocyclic compound in the form of compound I or II, or one of its single enantiomers or an alkaline salt thereof can be manufactured by compressing said units into tablets without significantly affecting the properties of the enteric coating layer. As explained above, if the enteric coating layer is damaged during compression of the enteric coating layered units the acid resistance of said enteric coating layer in the manufactured tablet will not be sufficient and the manufactured tablets will not fulfill standard requirements on enteric coated

articles, such as e.g. those defined in the United States Pharmacopeia, hereby incorporated in a whole by reference. In the following the expression "compounds I and II, respectively" is including the single enantiomers of said compounds as well as an alkaline salt of said compound or of one of its single enantiomers.

5

One object of the present invention is to provide a pharmaceutical multiple unit tableted dosage form comprising compound I or II or one of its single enantiomers or an alkaline salt thereof, in which the active substance is in the form of individually enteric coating layered units compressed into a tablet. The enteric coating layer(s) covering the individual units of active substance has properties such that the compression of the units into a tablet does not significantly affect the acid resistance of the individually enteric coating layered units. The active substance is prevented from degradation and dissolution in acidic media and has a good stability during long-term storage. The enteric coating layer covering the individual units disintegrates/dissolves rapidly in near neutral or alkaline media.

10
15

Another object of the present invention is to provide a pharmaceutical multiple unit tableted dosage form comprising compound I or II or one of its single enantiomers or an alkaline salt thereof which is suitable for press-through blister packages and which also has improved patient acceptance.

20

A further object of the present invention is to provide a multiple unit tableted dosage form comprising compound I or II or one of its single enantiomers or an alkaline salt thereof which is divisible and easy to handle. The multiple unit tableted dosage form may be dispersed in an aqueous liquid and can be given to patients with swallowing disorders and in pediatrics. Such a suspension of dispersed enteric coating layered units of appropriate size can be used for oral administration and also for feeding through a naso-gastric tube.

25

30

Detailed description of the invention.

The novel multiple unit tableted dosage form comprising compound I or II or one of its single enantiomers or an alkaline salt thereof is characterized in the following way. Individually enteric coating layered units containing the active substance, and optionally alkaline substances, are mixed with tablet excipients and compressed into multiple unit tableted dosage forms. With the expression "individual units" is meant small beads, particles, granules or pellets, in the following referred to as pellets.

10

The compaction process (compression) for formulating the multiple unit tableted dosage form must not significantly affect the acid resistance of the enteric coating layered pellets. In other words the mechanical properties, such as the flexibility and hardness as well as the thickness, of the enteric coating layer(s) must secure that the requirements on enteric coated articles in the United States Pharmacopeia are accomplished and that the acid resistance does not decrease more than 10 % during the compression of pellets into tablets.

20

The flexibility/hardness of enteric coating layers can be characterized for instance as Vickers hardness measured with a Shimadzu micro hardness indentation tester type HMV 2 000.

25

The acid resistance is defined as the amount of active substance in tablets or pellets after being exposed to simulated gastric fluid, USP, or to 0.1 M HCl(aq) relative to that of unexposed tablets or pellets, respectively. The test is accomplished in the following way. Tablets or pellets are exposed to simulated gastric fluid at a temperature of 37°C. The tablets disintegrate and release the enteric coating layered pellets to the medium. After two hours the pellets are removed and analyzed for content of active substance using High Performance Liquid Chromatography (HPLC). Presented values of acid resistance are averages of at least three individual determinations.

30

Core material

- The core material for the individually enteric coating layered pellets can be
- 5 constituted according to different principles. Seeds layered with active substance in the form of compounds I and II, respectively, or one of its single enantiomers or an alkaline salt thereof, optionally mixed with alkaline compounds, can be used as the core material for the further processing.
- 10 The seeds, which are to be layered with the active substance, can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or in mixtures or water soluble seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures. Further, the seeds may comprise active substance in the form of crystals,
- 15 agglomerates, compacts etc. The size of the seeds is not essential for the present invention and may vary between approximately 0.1 and 2 mm. The seeds layered with active substance are produced either by powder or solution/suspension layering using for instance granulating or spray coating/layering equipment.
- 20 Before the seeds are layered, the active substance may be mixed with further components. Such components can be binders, surfactants, fillers, disintegrating agents, alkaline additives or other pharmaceutically acceptable ingredients, alone or in mixtures. The binders are for example celluloses such as hydroxypropyl methylcellulose, hydroxypropyl cellulose and carboxymethylcellulose sodium,
- 25 polyvinyl pyrrolidone, sugars, starches and other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic or ionic surfactants such as for instance sodium lauryl sulfate.
- 30 Alternatively, the compounds I and II, respectively, optionally mixed with alkaline compounds and further mixed with suitable constituents can be

formulated into core material. Said core materials may be produced by extrusion/spheronization, balling or compression utilizing different process equipments. The size of the formulated core materials is approximately between 0.1 and 4 mm and preferably between 0.1 and 2 mm. The manufactured core materials can further be layered with additional ingredients comprising active substance and/or be used for further processing.

The active substance is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and a suitable concentration of the active substance in the final mixture. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives, can be used.

The active substance may also be mixed with an alkaline pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not restricted to, substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

Alternatively, the aforementioned core material can be prepared by using spray drying or spray congealing technique.

The active substance is in the form of 5-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole, 5-carbomethoxy-6-methyl-2-[(3,4-

dimethoxy-2-pyridinyl)methyl)sulfinyl-1H-benzimidazole, respectively, or one of its single enantiomers or an alkaline salt thereof. These compounds have an asymmetric centre in the sulfur atom, i.e. exists as two optical isomers (enantiomers). Both the pure enantiomers, racemic mixtures (50 % of each enantiomer) and unequal mixtures of the two enantiomers are suitable for the pharmaceutical formulation according to the present invention.

Enteric coating layer(s)

10

Before applying enteric coating layer(s) onto the core material in the form of individual pellets, said pellets may optionally be covered with one or more separating layers comprising pharmaceutical excipients optionally including alkaline compounds such as for instance pH-buffering compounds. This/these separating layer(s) separate(s) the core material from the outer layer(s) being enteric coating layer(s).

The separating layer(s) can be applied to the core material by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating process. As an alternative the separating layer(s) can be applied to the core material by using powder coating technique. The materials for separating layers are pharmaceutically acceptable compounds such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be included into the separating layer(s).

30

When the optional separating layer(s) is applied to the core material it may constitute a variable thickness. The maximum thickness of the optional separating layer(s) is normally only limited by processing conditions. The separating layer(s) may serve as a diffusion barrier and may act as a pH-buffering zone. The pH-buffering properties of the separating layer(s) can be further strengthened by introducing into the layer(s) substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance

5 $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ aluminium hydroxide/sodium bicarbonate coprecipitate or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, carbonic, citric or other suitable, weak, inorganic or organic acids; or

15 suitable organic bases, including basic amino acids and salts thereof. Talc or other compounds may be added to increase the thickness of the layer(s) and thereby strengthen the diffusion barrier. The optionally applied separating layer(s) is not essential for the invention. However the separating layer(s) may improve the chemical stability of the active substance and/or the physical properties of the

20 novel multiple unit tableted dosage form.

One or more enteric coating layers are applied onto the core material or onto the core material covered with separating layer(s) by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in

25 either water or in suitable organic solvents. As enteric coating layer polymers one or more separately or in combination of the following can be used; e.g. solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate,

30 carboxymethylethylcellulose, shellac or other suitable enteric coating layer polymer(s).

The enteric coating layers contain pharmaceutically acceptable plasticizers to obtain the desired mechanical properties, such as flexibility and hardness of the enteric coating layers. Such plasticizers are for instance, but not restricted to,
5 triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or other plasticizers.

The amount of plasticizer is optimized for each enteric coating layer formula, in relation to selected enteric coating layer polymer(s), selected plasticizer(s) and the
10 applied amount of said polymer(s), in such a way that the mechanical properties, i.e. flexibility and hardness of the enteric coating layer(s) for instance exemplified as Vickers hardness, are adjusted so that the acid resistance of the pellets covered with enteric coating layer(s) does not decrease significantly during the compression of pellets into tablets. The amount of plasticizer is usually above 10
15 % by weight of the enteric coating layer polymer(s), preferably 15 - 50 % and more preferably 20 - 50 %. Additives such as dispersants, colorants, pigments, polymers e.g. poly(ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be included into the enteric coating layer(s). Other compounds may be added to increase film thickness and to decrease diffusion of
20 acidic gastric juices into the acidic susceptible material.

To protect an acidic susceptible substance and to obtain an acceptable acid resistance of the multiple unit tableted dosage form according to the invention, the enteric coating layer(s) constitutes a thickness of approximately at least 10 μm ,
25 preferably more than 20 μm . The maximum thickness of the applied enteric coating layer(s) is normally only limited by processing conditions.

Over-coating layer

Pellets covered with enteric coating layer(s) may further be covered with one or more over-coating layer(s). The over-coating layer(s) can be applied to the enteric coating layered pellets by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating or layering process. The materials for over-coating layers are pharmaceutically acceptable compounds such as, for instance, sugar, polyethylene glycol, polyvinyl-pyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methyl cellulose, carboxymethyl-cellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be included into the over-coating layer(s). Said over-coating layer may further prevent potential agglomeration of coated pellets, further protect the enteric coating towards cracking during the compaction process and enhance the tableting process. The maximum thickness of the applied over-coating layer(s) is normally only limited by processing conditions.

Tablets

The enteric coating layered pellets are mixed with tablet excipients and compressed into a multiple unit tableted dosage form according to the present invention. The enteric coating layered pellets with or without an over-coating layer are mixed with tablet excipients such as fillers, binders, disintegrants, lubricants and other pharmaceutically acceptable additives and compressed into tablets. The compressed tablet is optionally coated with filmforming agent(s) to obtain a smooth surface of the tablet and further enhance the stability

of the tablet during packaging and transport. Such a tablet coating layer may further comprise additives like anti-tacking agents, colorants and pigments or other additives to obtain a tablet of good appearance.

- 5 The amount of enteric coating layered pellets constitutes less than 75% by weight of the total tablet weight and preferably less than 60 %. By choosing small enteric coating layered pellets in the formulation according to the present invention, the number of pellets in each tablet can be held high which in turn makes the tablet divisible with retained dosing accuracy.

10

- The mechanical properties, i.e. the flexibility and hardness of the enteric coating layer are essential for the acid resistance of the multiple unit tableted dosage form. The flexibility/hardness of the enteric coating layer surface may be characterized as a preliminary process parameter in the form of Vickers hardness, measured on enteric coating layered pellet(s) before compression of said pellets into tablets. The Vickers hardness may be measured with a Shimadzu micro hardness indentation tester type HMV 2000 (Micro Hardness Testing Machines for Vickers and Knoop Hardness JIS B 7734-1984 and JIS Z 2251-1980). The ability of the enteric coating layer(s) to withstand compression into tablets is, of course, a function of both the amount of applied coating layer and the mechanical properties of said coating layer material. To obtain well functioning enteric coating layered pellets with a reasonable amount of enteric coating layer material and which pellets can be compressed into tablets without significantly affecting the acid resistance, an enteric coating layer surface with a Vickers hardness of less than 8 is preferred. In case the pellets are covered with an over-coating layer the Vickers hardness of the enteric coating layer must be characterized before the over-coating layer is applied. A harder over-coating layer (Vickers hardness higher than 8) can be applied on top of a flexible and softer (Vickers hardness less than 8) enteric coating layer with retained acid resistance during compaction.

30

Thus, the formulation according to the invention consists of core material containing active substance in the form of compounds I and II, respectively mixed with alkaline compound(s), and excipients. The addition of an alkaline material may not be necessary, but such a substance may further enhance the stability of the active substance. The core material is optionally covered with one or more separating layer(s) optionally containing alkaline substance(s). The pellets, optionally covered with a separating layer(s), are then covered with one or more enteric coating layer(s) making the pellets insoluble in acidic media, but disintegrating/dissolving in near neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, the site where dissolution is wanted. The enteric coating layered pellets may further be covered with an over-coating layer before being formulated into the multiple unit tableted dosage form.

15

Process

The process for the manufacture of the dosage form represents a further aspect of the invention. The pharmaceutical processes can preferably be completely water-based and there are different descriptions given in the accompanying examples below.

20

Use of preparation

25

The preparation according to the invention is also especially advantageous in reducing gastric acid secretion. Such a multiple unit tableted dosage form is administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general the daily dose will be in the range of 1-1000 mg of active substance.

30

The preparation according to the present invention is also suitable for dispersion in an aqueous liquid with neutral or slightly acidic pH-value before being orally administered or fed through a naso-gastric tube.

5

The invention is illustrated more in detail by the following examples.

EXAMPLES

10 Example 1

Core material

5-Fluoro-2[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole sodium	312 g
Sugar sphere seeds	300 g
15 Hydroxypropyl methylcellulose	80 g
Purified water	1 520 g

Separating layer

Core material	300 g
20 Hydroxypropyl cellulose	21 g
Talc	37 g
Magnesium stearate	2 g
Purified water	400 g

25 Enteric coating layer

Pellets covered with separating layer	300 g
Methacrylic acid copolymer	285 g
Triethyl citrate	85.5 g
Mono- and diglycerides	14 g
30 Polysorbate 80	1 g
Purified water	557 g

Tablets

Enteric coating layered pellets	150 g
Microcrystalline cellulose	349 g

Sodium stearyl fumarate

1 g

Solution layering is performed in a fluid bed apparatus using bottom spray technique. 5-Fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole sodium is sprayed onto sugar sphere seeds from a water solution containing the dissolved binder. The size of sugar sphere seeds are in the range of
5 0.25 to 0.35 mm.

The prepared core material is covered with separating layer in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer is sprayed as a water dispersion
10 onto the pellets covered with separating layer in a fluid bed apparatus. The Vickers hardness on enteric coating layered pellets is measured to a value of 2.

Enteric coating layered pellets and tablet excipients are mixed and compressed into tablets using a single punch tableting machine using 12 mm round punches.
15 Hardness of tablet measured on a Schleuniger hardness tester is determined to 95 - 116 N.

Example 2

20 Core material

5-Carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium	600 g
Mannitol	1000 g
Microcrystalline cellulose	300 g
25 Hydroxypropyl cellulose	100 g
Sodium lauryl sulfate	6 g
Purified water	802 g

Separating layer

30 Core material	400 g
Hydroxypropyl methylcellulose	48 g
Purified water	960 g

Enteric coating layer

	Pellets covered with separating layer	200 g
	Methacrylic acid copolymer	100 g
	Triethyl citrate	30 g
5	Mono- and diglycerides	5 g
	Polysorbate 80	0.5 g
	Purified water	309 g

Tablets

10	Enteric coating layered pellets	200 g
	Microcrystalline cellulose	299 g
	Sodium stearyl fumarate	1.2 g

- Sodium lauryl sulfate is dissolved in purified water to form the granulation liquid. 5-
 15 Carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole magnesium, mannitol, microcrystalline cellulose and hydroxypropyl cellulose are dry-mixed. The granulation liquid is added to the powder mixture and the mass is wet-mixed.
- 20 The wet mass is forced through an extruder equipped with screens, aperture size 0.5 mm. The extrudate is spheronized on a friction plate in a spheronizing apparatus. The core material is dried in a fluid bed dryer and classified. The prepared core material is covered with separating layer in a fluid bed apparatus with a hydroxypropyl methyl-cellulose/water solution.
- 25 The enteric coating layer is applied to the pellets covered with separating layer from an aqueous dispersion of methacrylic acid copolymer plasticized with triethyl citrate to which a mono- and diglycerides/polysorbate dispersion has been added. The pellets are dried in a fluid bed apparatus.
- 30 Enteric coating layered pellets, microcrystalline cellulose and sodium stearyl fumarate are mixed and compressed into tablets with a tablet weight corresponding to 20 mg active substance, using a single punch tableting machine equipped with 10 mm round punches.

Example 3Core material

	(-)-5-Carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole magnesium	600 g
5	Sugar sphere seeds	600 g
	Hydroxypropyl methylcellulose	150 g
	Colloidal silicon dioxide	4 g
	Purified water	1 800 g

10

Separating layer

	Core material	500 g
	Hydroxypropyl cellulose	40 g
	Talc	67 g
15	Magnesium stearate	6 g
	Purified water	800 g

Enteric coating layer

	Pellets covered with separating layer	500 g
20	Methacrylic acid copolymer	200 g
	Triethyl citrate	60 g
	Purified water	392 g

Tablets

25	Enteric coating layered pellets	430 g
	Microcrystalline cellulose	871 g
	Sodium stearyl fumarate	3 g

30 (-)-5-Carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole magnesium, part of the hydroxypropyl methylcellulose and colloidal silicon dioxide are dry-mixed forming a powder mixture. Sugar sphere seeds (0.25-0.35 mm) are layered with the powder in a centrifugal fluidized coating granulator while spraying a hydroxypropyl methylcellulose solution (6 %, w/w).

35 The prepared core material is dried and covered with separating layer in a centrifugal fluidized coating granulator. A fluid bed apparatus is used for enteric coating layering.

Enteric coating layered pellets and tablet excipients are mixed and compressed into tablets using a rotary tableting machine equipped with 6 pairs of 10 mm round punches. The amount of active substance in the tablet is approx. 20 mg.

5

Example 4

10 Core material

(-)-5-Carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole	400 g
Silicon dioxide seeds	400 g
Hydroxypropyl methylcellulose	100 g
15 Sodium lauryl sulfate	2 g
Purified water	2 000 g

Separating layer

Core material	800 g
20 Hydroxypropyl methylcellulose	65 g
Purified water	1 300 g

Enteric coating layer

Pellets covered with separating layer	500 g
25 Methacrylic acid copolymer	300 g
Polyethylene glycol 400	60 g
Mono- and diglycerides	9 g
Polysorbate 80	1 g
Purified water	800 g

30

Tablets

Enteric coating layered pellets	200 g
Microcrystalline cellulose	598 g
Sodium stearyl fumarate	2 g

35

Suspension layering is performed in a fluid bed apparatus. (-)-5-Carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole is sprayed onto the

seeds of silicon dioxide (size range 0.15 - 0.3 mm) from a water suspension containing the dissolved binder and a surface active ingredient.

5 The prepared core material is covered with separating layer in a fluid bed apparatus using a hydroxypropyl methylcellulose solution. The enteric coating layer material is sprayed as a water dispersion onto pellets in a fluid bed apparatus. Enteric coating layered pellets and the tableting excipients are mixed and compressed into tablets as described in Example 1.

10 Example 5

Enteric coating layer

Pellets covered with separating layer (manufacturing and composition as in Example 1)

	500 g
15 Methacrylic acid copolymer	250 g
Polyethylene glycol 6000	75 g
Mono- and diglycerides	12.5 g
Polysorbate 80	1.2 g
Purified water	490 g

20

Tablets

Enteric coating layered pellets	600 g
Microcrystalline cellulose	1 395 g
Sodium stearyl fumarate	5 g

25

Enteric coated pellets, microcrystalline cellulose and sodium stearyl fumarate are mixed and compressed into tablets as described in Example 3.

Example 6

30

Enteric coating layer

Pellets covered with separating layer (manufacturing and composition as in Example 1)

	400 g
Hydroxypropyl methylcellulose phthalate	400 g
35 Diethyl phthalate	80 g
Ethanol	1 600 g
Acetone	4 000 g

Tablets

	Enteric coating layered pellets	500 g
	Microcrystalline cellulose	1 500 g
5	Magnesium stearate	5 g

Enteric coating layering is performed by spaying a solution in a fluid bed. Enteric coating layered pellets, microcrystalline cellulose and magnesium stearate are mixed and compressed into tablets as described in Example 3.

10

Example 7Core material

	(+)-5-Fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-	
15	benzimidazole	400 g
	Sugar sphere seeds (non-pareils)	400 g
	Hydroxypropyl methylcellulose	80 g
	Purified water	1 600 g

20 Separating layer

	Core material	800 g
	Hydroxypropyl cellulose	40 g
	Talc	40 g
	Magnesium stearate	8 g
25	Purified water	800 g

Enteric coating layer

	Pellets covered with separating layer	800 g
	Methacrylic acid copolymer	400 g
30	Triethyl citrate	120 g
	Mono- and diglycerides	8 g
	Polysorbate 80	1 g
	Purified water	800 g

35 Tablets

	Enteric coating layered pellets	1 000 g
	Dibasic calcium phosphate anhydrous	1 760 g

Microcrystalline cellulose	440 g
Magnesium stearate	16 g

5 Suspension layering is performed in a fluid bed apparatus. (+)-5-Fluoro-2-[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole is sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder.

10 The prepared core material is covered with separating layer in a fluid bed with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer is sprayed as a dispersion onto the pellets covered with separating layer in a fluid bed. Enteric coating layered pellets, dibasic calcium phosphate anhydrous in granulated form, microcrystalline cellulose and magnesium stearate are mixed and compressed into tablets as described in Example 3.

Example 8

15

Tablets

Enteric coating layered pellets (manufacturing and composition as in Example 2)

	1.00 kg
Microcrystalline cellulose	1.45 kg
20 Anhydrous lactose	0.14 kg
Starch	0.23 kg
Povidone	0.18 kg
Purified water	0.836 kg

25 Povidone is dissolved in water. Microcrystalline cellulose, anhydrous lactose and starch are dry-mixed. The povidone solution is added while wet-mixing. The wet mass is dried in an oven. The granulated mass is milled using an oscillating granulator.

30 Enteric coating layered pellets and the prepared granulate are mixed and compressed into engraved and scored tablets using a rotary tableting machine equipped with 16 pairs of oval, 8.5x17 mm, tablet punches.

Example 9Over-coating layer

5	Enteric coating layered pellets (manufacturing and composition as in Example 7)	400 g
	Hydroxypropyl methylcellulose	120 g
	Purified water	2 280 g

Tablets

10	Over-coating layered pellets	100 g
	Microcrystalline cellulose	233 g

15 In a fluid bed apparatus a hydroxypropyl methylcellulose solution is sprayed onto enteric coating layered pellets. The Vickers hardness on the enteric coating layered pellets before applying the over-coating layer is 2 and the Vickers hardness measured on the over-coating layered pellets is 11. Pellets covered with over-coating layer and microcrystalline cellulose are mixed and compressed into tablets as described in Example 2.

Example 10

20

Core material

	5-Fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole magnesium	150 g
	Sugar sphere seeds	200 g
25	Hydroxypropyl methylcellulose	75 g
	Purified water	1 500 g

Separating layer

	Core material	380 g
30	Hydroxypropyl cellulose	38 g
	Talc	65 g
	Magnesium stearate	5 g
	Purified water	760 g

35 Enteric coating layer

	Pellets covered with separating layer	150 g
	Methacrylic acid copolymer	60 g

Triethyl citrate	18 g
Mono- and diglycerides	3 g
Polysorbate 80	0.3 g
Purified water	117 g

5

Tablets

Enteric coating layered pellets	90 g
Microcrystalline cellulose	209 g
Sodium stearyl fumarate	1 g

10 Suspension layering is performed in a fluid bed apparatus. 5-Fluoro-2[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole magnesium is sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder.

15 The prepared core material is covered with separating layer in a fluid bed apparatus. The enteric coating layer is sprayed as a water dispersion onto the pellets covered with separating layer in a fluid bed apparatus.

Enteric coating layered pellets and tablet excipients are mixed and compressed into tablets using a single punch tableting machine using 8 mm round punches. Tablet hardness measured on a Schleuniger hardness tester is determined to 95 - 109 N.

20

Example 11Enteric coating layer

Core material (no separating layer)	500 g
25 Methacrylic acid copolymer	500 g
Triethyl citrate	150 g
Mono- and diglycerides	25 g
Polysorbate 80	2.5 g
Purified water	978 g

30

Tablets

	Enteric coating layered pellets	800 g
	Microcrystalline cellulose	1 860 g
5	Sodium stearyl fumarate	7 g

Core material is produced as in Example 7.

Enteric coating layered pellets and tablet excipients are compressed as described in Example 3.

10

Example 12

15

Enteric coating layer

	Pellets covered with separating layer	200 g
	Hydroxypropyl methylcellulose acetate succinate	150 g
	Triethyl citrate	55 g
20	Ethanol	1 200 g
	Purified water	300 g

Tablets

	Enteric coating layered pellets	300 g
	Microcrystalline cellulose	700 g

The pellets covered with separating layer are produced according to Example 10.

25 The enteric coating layer is sprayed as a solution onto the pellets.

Enteric coating layered pellets and microcrystalline cellulose are mixed and compressed into tablets as described in Example 1.

Example 13

30

Core material

	(+)-5-Fluoro-2[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole magnesium	200 g
--	--	-------

	Sugar sphere seeds	200 g
	Hydroxypropyl cellulose	75 g
	Purified water	1 500 g
5	<u>Separating layer</u>	
	Core material	380 g
	Hydroxypropyl cellulose	38 g
	Talc	65 g
	Magnesium stearate	5 g
10	Purified water	760 g

	<u>Enteric coating layer</u>	
15	Pellets covered with separating layer	200 g
	Methacrylic acid copolymer	150 g
	Triethyl citrate	45 g
	Mono- and diglycerides	4 g
	Polysorbate 80	0.4 g
20	Purified water	300 g

Tablets

	Enteric coating layered pellets	100 g
	Microcrystalline cellulose	250 g
	Sodium stearyl fumarate	1 g

25 Suspension layering is performed in a fluid bed apparatus. (+)-5-Fluoro-2[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole magnesium is sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder.

30 The prepared core material is covered with separating layer in a fluid bed apparatus. The enteric coating layer is sprayed as a water dispersion onto the pellets covered with separating layer in a fluid bed apparatus.

Enteric coating layered pellets and tablet excipients are mixed and compressed into tablets using 10 mm round punches.

Example 14Enteric coating layer

5	Pellets covered with separating layer	200 g
	Methacrylic acid copolymer	200 g
	Triethyl citrate	60 g
	Mono- and diglycerides	10 g
	Polysorbate 80	1 g
10	Purified water	391 g

Over-coating layer

	Enteric coating layered pellets	471 g
15	Hydroxypropyl methylcellulose	6 g
	Magnesium stearate	0.2 g
	Purified water	120 g

Tablets

20	Over-coating layered pellets	140 g
	Microcrystalline cellulose	114 g
	Sodium stearyl fumarate	0.4 g

- Pellets covered with separating layer are produced according to Example 13.
- 25 The enteric coating layer and the over-coating layer are sprayed onto pellets in a fluid bed apparatus. Over-coating layered pellets and tablet excipients are compressed using a single punch (round, 12 mm) tableting machine.

Example 15

30

Enteric coating layer

	Pellets covered with separating layer	200 g
	Methacrylic acid copolymer	40 g
	Triethyl citrate	12 g
35	Mono- and diglycerides	2 g
	Polysorbate 80	0.2 g
	Purified water	78 g

Over-coating layer

	Enteric coating layered pellets	200 g
	Hydroxypropyl methylcellulose	4 g
5	Magnesium stearate	0.1 g

Tablets

	Over-coating layered pellets	69 g
	Microcrystalline cellulose	230 g
10	Sodium stearyl fumarate	0.7 g

Pellets covered with separating layer are produced according to Example 13.

- 15 The enteric coating layer and the over-coating layer are sprayed onto pellets in a fluid bed apparatus. The amount of enteric coating layer material used in this example corresponds to an enteric coating layer thickness of approx. 20 μ m. Over-coating layered pellets and tablet excipients are compressed using a single punch (round, 10 mm) tableting machine.

20 Example 16Enteric coating layer

	Pellets covered with separating layer	500 g
	Cellulose acetate phthalate	375 g
25	Diethyl phthalate	150 g
	Acetone	2 000 g
	Ethanol	2 000 g

Tablets

	Enteric coating layered pellets	100 g
	Microcrystalline cellulose	300 g
	Crospovidone	8 g
	Sodium stearyl fumarate	1 g

- 30 The pellets covered with separating layer are produced as in Example 13.

The enteric coating layer is applied in a fluid bed from a acetone/ethanol solution. Enteric coating layered pellets and tablet excipients are mixed and compressed into tablets as described in Example 2.

5 Example 17

Core material

	5-Carbomethoxy-6-methyl-2[[[(3,4-dimethoxy-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole	200 g
10	Sugar sphere seeds	200 g
	Hydroxypropyl cellulose	25 g
	Purified water	623 g

Separating layer

15	Core material	200 g
	Hydroxypropyl cellulose	20 g
	Talc	34 g
	Magnesium stearate	3 g
	Purified water	457 g

20

Enteric coating layer

	Pellets covered with separating layer	200 g
	Methacrylic acid copolymer	150 g
	Triethyl citrate	45 g
25	Mono- and diglycerides	8 g
	Polysorbate 80	1 g
	Purified water	250 g

Tablets

	Enteric coating layered pellets	100 g
	Microcrystalline cellulose	232 g
	Sodium stearyl fumarate	1 g

- 30 Suspension layering is performed in a fluid bed apparatus using bottom spray technique. 5-Carbomethoxy-6-methyl-2[[[(3,4-dimethoxy-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole is sprayed onto sugar sphere seeds from a

water solution containing the dissolved binder.

The prepared core material is covered with separating layer in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer is sprayed as a water dispersion onto the pellets covered with separating layer in a fluid bed apparatus.

Enteric coating layered pellets and tablet excipients are mixed and compressed into tablets using a single punch tableting machine (Korsch EK0) using 11 mm round punches. Tablet hardness measured on a Schleuniger hardness tester is determined to approx. 170 N.

Example 18

The same tableted dosage form as described in Example 17 is produced with (+)-5-carbomethoxy-6-methyl-2[[[(3,4-dimethoxy-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium as active substance.

The results from tests on acid resistance of the enteric coating layered pellets and the compressed tablets are disclosed in Table I, below.

Table I

Example No	Acid resistance, pellets (%)	Acid resistance, tablets (%)
1	95	93
10	95	86

Comments:

Surprisingly, the acid resistance, tablets, shows that the enteric coating layer according to the present invention sufficiently withstands compression.

Reference example ITablets

	Omeprazole enteric coating layered pellets	180 g
5	Microcrystalline cellulose	219 g
	Sodium stearyl fumarate	1 g

10 Omeprazole pellets from Losec® 40 mg capsules are mixed with microcrystalline cellulose and sodium stearyl fumarate and compressed into tablets using a single punch tableting machine. The Vickers hardness on the enteric coating layered pellets is measured to a value of 22. The tablet tooling is round with a diameter of 10 mm. Punch force is set to 3.7 kN.

15

Reference example IITablets

	Lansoprazole enteric coating layered pellets	276 g
20	(content of Lanzo® 30 mg capsules)	
	Microcrystalline cellulose	644 g

25 Lansoprazole pellets are mixed with microcrystalline cellulose and tableted in a single punch tableting machine. The Vickers hardness on enteric coating layered pellets is measured to a value of 18. The tablet tooling is round with a diameter of 12 mm. Punch force is set to 3.6 kN.

Reference example III30 Core material

	Magnesium omeprazole	15.0 kg
	Sugar sphere seeds	15.0 kg
	Hydroxypropyl methylcellulose	2.25 kg
	Purified water	40 kg

35

Separating layer

	Core material	15.0 kg
	Hydroxypropyl cellulose	1.5 kg
	Talc	2.57 kg
5	Magnesium stearate	0.21 kg
	Purified water	30 kg

Enteric coating layer

- 10 Pellets covered with separating layer 200 g
- Enteric coating layer material is used as described in Drugs Made In Germany 37, No. 2 (1994), p.53, Table 1, Formulation no. 9.
- The amount of coating polymer as calculated in above reference is 40 % (w/w).

15 Over-coating layer

	Enteric coating layered pellets	291 g
	Hydroxypropyl methylcellulose	4 g
	Magnesium stearate	0.2 g
20	Purified water	80 g

Tablets

	Over-coating layered pellets	75 g
	Microcrystalline cellulose	174 g
25	Sodium stearyl fumarate	0.6 g

- 30 Suspension layering is performed in a fluid bed apparatus. Omeprazol magnesium is sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder. The separating layer, enteric coating layer and the over-coating layer are sprayed onto pellets in a fluid bed apparatus. The over-coating layer is applied to prevent sticking of pellets before tableting. Over-coating layered pellets and tablet excipients are tableted as in Example 2. Upper punch force is set to 5 kN.

- 35 The results from tests on acid resistance of the enteric coating layered pellets and the compressed tablets are disclosed in Table II, below.

Table II

Reference example number	Acid resistance pellets (%),	Acid resistance tablets (%),
I	97	6
II	98	25
III	98	82

Comments:

As can be seen from the presented data, the enteric coating layer of the products studied, including the two marketed products (Reference examples I and II) do not possess the mechanical properties required to withstand compression into tablets.

Preparation of active substance

5-Fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole magnesium and 5-carbomethoxy-6-methyl-2-[[[3,4-demethoxy-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole used in the examples are disclosed in WO 90/06925 and WO 91/19712, hereby incorporated as a whole by references. Some of the single enantiomers thereof are prepared in accordance with the following Examples A - E.

Example A. Preparation of (+)-5-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

The crude product of the diastereomers of a mixture of two regioisomeric mandelic esters, namely 5-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole and 6-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole (5.0 g, 9.8 mmol) were divided into five parts and each part was chromatographed on a reversed phase column (HPLC, Kromasil C8) in order to separate the diastereomers. The stereo isomers were easily separated by elution with a mixture of aqueous 0.1 M ammonium acetate and acetonitrile (67.5/32.5). However each separated diastereomer consisted of a mixture of the two regioisomers. These intermediates were used directly in their

solutions during the hydrolysis step. To the acetonitrile/aqueous solutions of the more lipophilic diastereomer were added 1 M aqueous solutions of NaOH until the pH was around 12-13. After 5 minutes the solutions were neutralized with 3.0 M aqueous solutions of NH₄Cl whereupon the solutions from each preparation were combined and extracted with methylene chloride. The organic phases were dried over Na₂SO₄ and the solvents were removed by film evaporation. Addition of 30 ml of acetonitrile afforded the product to crystallize and after filtration there was obtained 260 mg (16%) of the title compound as white crystals, m.p. 152°-154°C. The optical purity (e.e.) which was analyzed by chiral column chromatography was 99.2%. $[\alpha]^{20}_D = +208.6^\circ$ (c=0.5%, chloroform).

Example B. Preparation of (+)-5-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

Magnesium (7.1 mg, 0.29 mmol) is dissolved and reacted with methanol at 40°C with a catalytic amount of methylene chloride. The reaction is run under nitrogen and is finished after two hours. (+)-5-Fluoro-2-[[[4-cyclo-propylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (200 mg, 0.58 mmol) obtained as in Example A was added after the magnesium methoxide solution had been chilled to room temperature. The mixture is stirred for two hours whereupon a small amount of water (0.05 ml) is added. After stirring another hour the small amount of inorganic salts are filtered off. The solution is concentrated on a rotavapor until two ml of the solution is left. While chilling and stirring, water is added dropwise which afforded the product to precipitate. After filtration the product is washed with a small amount of water and then dried in vacuum. There is obtained 97 mg (47%) of the title compound as a white powder. $[\alpha]^{20}_D = +191.3^\circ$ (c=1.0%, DMSO).

Example C. Preparation of (+)-5-carbomethoxy-6-methyl-2-[[[3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

The crude product of the diastereomers of a mixture of two regioisomeric mandelic esters, namely 5-carbomethoxy-6-methyl-2-[[[3,4-dimethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole and 6-carbomethoxy-5-methyl-2-[[[3,4-dimethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole (1.8 g, 3.3 mmol) was divided into three parts. Each part was chromatographed on a reversed phase column (HPLC, Kromasil C8) in order to separate the diastereomers. The

stereoisomers were easily separated by elution with a mixture of aqueous 0.1 M ammonium acetate and acetonitrile (70/30), but each separated diastereomer consisted of a mixture of the two regioisomers. These intermediates were used directly in their solutions during the hydrolyses; To the acetonitrile/aqueous solutions of the more lipophilic diastereomer were added 1 M aqueous solutions of NaOH until the pH was around 12-13. After 5 minutes the solutions were neutralized with 3.0 M aqueous solutions of NH₄Cl. The solutions from each preparation were combined and extracted with methylenechloride whereupon the organic phases were dried over Na₂SO₄. Removal of the solvents and flash chromatography of the residue (silica gel, methanol-methylenechloride gradient 1-8%) yielded 250 mg of a yellow oil. The product was crystallised by adding acetonitrile (3 ml) and after filtration there was obtained 210 mg (32%) of the title compound as white crystals m.p. 171-173° C. $[\alpha]^{20}_D = +153.1^\circ$ (c=0.5%, chloroform).

Example D. Preparation of (+)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

To a mixture of (+)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (200 mg, 0.51 mmol) and ethanol (10 ml) was added an aqueous solution of 2.0 M NaOH (0.26 ml, 0.51 mmol). The solvent was removed by film evaporation whereupon the residue was dissolved in 2-butanone (1 ml). Toluene (5 ml) was added dropwise while stirring. The formed precipitate was removed by centrifugation and washed with diethyl ether. There was obtained 170 mg (81%) of the title compound as white crystals m. p. (decomp.) 170°-173°C. $[\alpha]^{20}_D = +93.6^\circ$ (c=1%, methanol).

Example E. Preparation of (+)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

(+)-5-Carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt (100 mg, 0.24 mmol) obtained as in Example D is dissolved in water (2 ml) and MgCl₂·6H₂O (25 mg, 0.12 mmol) dissolved in water (1 ml) is added dropwise. The formed precipitate is isolated by centrifugation and washed with water. The product is dried in a desiccator and there is obtained 84 mg (87%) of a white powder. $[\alpha]^{20}_D = +170^\circ$ (c=0.5%, DMSO).

CLAIMS

1. An oral pharmaceutical multiple unit tableted dosage form comprising tablet excipients and individually enteric coating layered units of a core material
5 containing active substance in the form of 5-fluoro-2[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole or 5-carbomethoxy-6-methyl-2[[[3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or one of its single enantiomers or an alkaline salt thereof, optionally mixed with alkaline compounds, covered with one or more layer(s) of which at least one is an enteric
10 coating layer, whereby the enteric coating layer has mechanical properties such that the compression of the individual units mixed with the tablet excipients into the multiple unit tableted dosage form does not significantly affect the acid resistance of the individually enteric coating layered units.
- 15 2. A tableted dosage form according to claim 1, wherein the active substance is 5-fluoro-2[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or one of its single enantiomers or an alkaline salt thereof.
- 20 3. A tableted dosage form according to claim 1, wherein the active substance is 5-carbomethoxy-6-methyl-2[[[3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or one of its single enantiomers or an alkaline salt thereof.
- 25 4. A tableted dosage form according to claim 1, wherein the acid resistance of the individually enteric coating layered units is in coherence with the requirements on enteric coated articles defined in the United States Pharmacopeia.
- 30 5. A tableted dosage form according to claim 1, wherein the acid resistance of the individually enteric coating layered units does not decrease more than 10 % during the compression of the individual units into the multiple unit tableted dosage form.

6. A tableted dosage form according to claim 1, wherein the enteric coating layer covering the individual units comprises a plasticized enteric coating layer material.

5

7. A tableted dosage form according to claim 1, wherein the enteric coating layer covering the individual units has a thickness of at least 10 μm .

8. A tableted dosage form according to claim 1, wherein the individually enteric coating layered units are further covered with an over-coating layer comprising pharmaceutically acceptable excipients.

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9. A tableted dosage form according to claim 1, wherein the dosage form is divisible.

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10. A tableted dosage form according to claim 1, wherein the dosage form is dispersible to a suspension of individually enteric coating layered units in an aqueous liquid.

11. A tableted dosage form according to claim 1, wherein an optionally applied separating layer(s) comprises pharmaceutically acceptable excipients which are soluble, or insoluble but disintegrating in water, and optionally alkaline compounds.

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12. A tableted dosage form according to claim 1, wherein the core material is a seed layered with the active substance.

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13. A tableted dosage form according to claim 12, wherein the seeds have a size of 0.1 - 2 mm.

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14. A process for the manufacture of a pharmaceutical multiple unit tableted dosage form comprising tablet excipients and individually enteric coating layered units of a core material containing active substance as defined in claim 1, optionally mixed with alkaline compounds, wherein the core material is
- 5 optionally covered with one or more separating layer(s) and further covered with one or more enteric coating layer(s), whereafter the individually enteric coating layered units are mixed with tablet excipients and compressed into a tablet, and whereby the enteric coating layer has mechanical properties such that the compression of the individual units with the tablet excipients into the multiple
- 10 unit tableted dosage form does not significantly affect the acid resistance of the individually enteric coating layered units.
15. A process according to claim 14, wherein the individually enteric coating layered units are further coated with an over-coating layer before compression of
- 15 the individual units into the multiple unit tableted dosage form.
16. A tableted dosage form according to any of claims 1 to 13 for use in therapy.
17. A tableted dosage form according to any of claims 1 to 13 for use in inhibiting
- 20 gastric acid secretion in mammals and man.
18. A tableted dosage form according to any of claims 1 to 13 for use in the treatment of gastrointestinal inflammatory diseases in mammals and man.
- 25 19. A method for inhibiting gastric acid secretion in mammals and man by administering to a host in need thereof a therapeutically effective dose of a multiple unit tableted dosage form according to any of claims 1 to 13.
20. A method for the treatment of gastrointestinal inflammatory diseases in
- 30 mammals and man by administering to a host in need thereof a therapeutically effective dose of a multiple unit tableted dosage form according to any of claims

1 to 13.

21. A press-through blister package comprising a multiple unit tableted dosage form according to any of claims 1 to 13.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 95/00680

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/26, A61K 9/20, A61K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE, MEDLINE, WPI, WPIL, CLAIMS, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0247983 A2 (AKTIEBOLAGET HÄSSLE), 2 December 1987 (02.12.87), page 5, line 6 - page 9, line 12, examples --	1-18,21
X	EP 0519144 A1 (ILSAN ILAC VE HAMMADELERI SANAYI A.S.), 23 December 1992 (23.12.92) --	1-18,21
A	EP 0365947 A1 (PHARMACIA AB), 2 May 1990 (02.05.90), page 3, line 37 - line 55 --	1-18,21
A	WO 9222284 A1 (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH), 23 December 1992 (23.12.92) -- -----	1-18,21

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search

Date of mailing of the international search report

13 October 1995

21.10.1995

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 95/00680

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 19-20
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SE 95/00680

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A2- 0247983	02/12/87	SE-T3- 0247983 AU-B- 601974 AU-A- 7191287 CA-A- 1292693 DE-A- 3783394 DK-B- 169988 EP-A, A, A 0496437 EP-A, A- 0567201 ES-T- 2006457 GB-A- 2189698 HK-A- 135294 IE-B- 61416 JP-C- 1863556 JP-A- 5294831 JP-A- 62258320 NO-B, C- 174239 SU-A- 1820837 US-A- 4786505	27/09/90 05/11/87 03/12/91 18/02/93 24/04/95 29/07/92 27/10/93 01/01/94 04/11/87 09/12/94 02/11/94 08/08/94 09/11/93 10/11/87 27/12/93 07/06/93 22/11/88
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PCTWORLD INTELLECTU
Inter

WO 9602236A1

INTERNATIONAL APPLICATION PUBLISHED

(51) International Patent Classification⁶ :A61K 9/20, 9/16, 31/29, 31/65, 31/415,
31/43, 31/71, 31/44, B01J 13/10, A61J
3/00

A1

(11) International Publication Number:

WO 96/02236

(43) International Publication Date:

1 February 1996 (01.02.96)

(21) International Application Number: PCT/AU95/00434

(22) International Filing Date: 18 July 1995 (18.07.95)

(30) Priority Data:

PM 6952

20 July 1994 (20.07.94)

AU

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NSW 2046 (AU).(74) Agent: SHELSTON WATERS; 60 Margaret Street, Sydney,
NSW 2000 (AU).(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH,
CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE,
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TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT,
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PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN,
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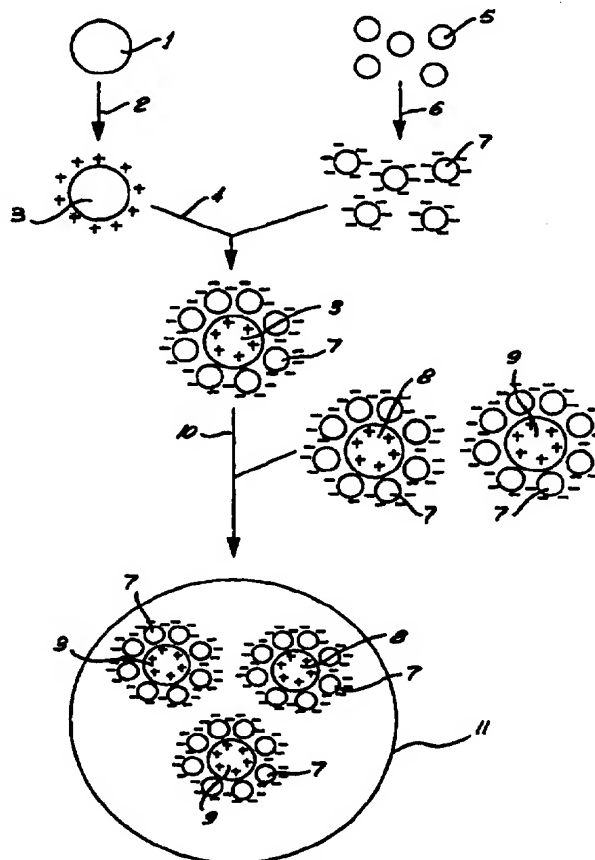
Published

With international search report.

(54) Title: IMPROVED COMBINATION DOSE UNIT

(57) Abstract

This invention relates to a combination therapy dose unit and a method of preparing such a dose unit. The method of preparation is designed to prevent interaction between a plurality of active agents in a combination therapy dose unit, and comprises the steps of charging particles of an active agent, charging particles of an inert particulate medium with a charge of opposite polarity to that of the charged particles of the active agent and allowing the charged inert particulate medium particles to electrostatically adhere to the charged particles of the active agent, thereby to coat the active agent with inert particulate medium. Thereafter other active agents can be treated in a similar manner and the electrostatically coated active agents can be combined, and may include other non-coated active agents, into a single combination therapy dose unit such as a tablet.



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TITLE: "IMPROVED COMBINATION DOSE UNIT"**TECHNICAL FIELD**

This invention relates to an improved combination medication, a process of manufacturing such a medication and therapeutic methods using such a medication.

Although the invention will be described with reference to a medication for treating gastrointestinal disorders associated with *Helicobacter pylori*, it is to be understood that it may be adapted to other forms of combined medication or therapy. Such variations will be within the knowledge of those skilled in the art and the scope of the invention.

BACKGROUND ART

"Triple Therapy" is a multiple-part therapy for gastrointestinal or stomach ulcers resulting from infection by *H. pylori*. The method involves the administration of tablets or capsules of a bismuth compound and two types of antibiotics for eg. 12 days. In a five-times per day regimen, a patient ingests 15 tablets or capsules, making it a tedious and complicated protocol and may reduce compliance and hence efficacy of treatment.

The recommended dosage of each active component in "Triple Therapy" is:

- bismuth subcitrate (108 mg) or bismuth subsalicylate (260 mg);
- tetracycline HCl (250 mg) or amoxycillin (500 mg) and metronidazole (250 mg).

It has hitherto not been possible to combine all three of the active agents into a single dose unit such as a tablet or capsule.

One problem is that the mass of a single capsule or tablet which contains the three agents will, in the absence of necessary excipients or auxiliaries, already be great and far exceed the maximal mass of components allowed for the production of a reasonably sized tablet/capsule. In addition such a mass cannot be expected to be ingested or swallowed by most patients without difficulty.

A second problem relates to cross-reactions and degradation. In a single unit containing the three agents in the presence of water of hydration and residual oxygen, ongoing oxidation will result in the degradation and/or inactivation of the active components and concomitantly lead to production of undesirable, toxic by-products. For instance, bismuth subsalicylate may oxidise to form a product which escapes from the bowel into the brain and ultimately cause encephalopathy. Tetracycline HCl degrades with time to form unwanted 4-epi-tetracycline and a side product which is toxic to the kidneys. The cross-reactivity between the agents also create a further problem by increasing the levels of undesirable by-products. Thus, if a single unit were to be stored in a warehouse or on a pharmacist's shelf, the risk of obtaining a therapeutically inactive but toxic composition is high.

It has been suggested that the three agents may each be micro-encapsulated as separate microspheres which are then incorporated into a single capsule. However, the high dosage of each component and the large volume of "empty space" between the thickly coated microcapsules render the production of a capsule that is easily swallowed and within the bounds of manufacturing standards impractical. The minimum effective dose of the combined agents is more than 600 mg and far exceeds the maximum practical mass for a capsule, even if it is elongated.

Furthermore, orally ingested bismuth compounds stain the oral mucosa a brown colour. It is therefore desirable to obtain a product which does not dissolve in the mouth but which is capable of dissolving rapidly within the stomach.

The present invention ameliorates one or more of the disadvantages described above.

SUMMARY OF THE INVENTION

In a first aspect, the invention consists in a method of preventing interaction between a plurality of active agents at risk of interacting in a combination therapy dose unit, said method comprising the steps of:

- (i) charging particles of a first active agent,
- (ii) charging particles of an inert particulate medium with a charge of opposite polarity to that of the charged particles of the first active agent,
- (iii) allowing the charged inert particulate medium particles to electrostatically adhere to the charged particles of the first active agent thereby to coat the active agent with inert particulate medium; and
- (iv) combining the coated first active agent particles with other active agents of the dose unit.

In the second aspect, the invention consists in a combination therapy dose unit comprising at least one active agent which has been coated with an inert particulate medium according to the method described above.

A third aspect of the invention relates to a method of preventing or treating a disorder in a host requiring administration of a plurality of active agents comprising the administration of a combination therapy dose unit as described above.

In a preferred embodiment the medium which is in electrostatic communication with an active agent includes magnesium stearate, silicon dioxide or other inert or lubricating material. Such a medium is preferably electrically charged by using the principles of static electricity. For instance, the medium may be passed over a negative electrode at extra high tension ("EHT") or high voltage and very low current to render the medium negatively charged.

In another preferred aspect, the invention provides a dose unit as described above, in combination with a micro-encapsulated proton pump inhibitor.

The invention will now be described by way of example to illustrate preferred embodiments only and is not intended to limit the scope in any way.

BRIEF DESCRIPTION OF THE FIGURE

Figure 1 shows a preferred process of making a combination therapy dose unit.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In Figure 1, a microparticle of a first active agent 1, such as bismuth subsalicylate, and containing a polyvinylpyrrolidone binder, a lactose filler and an exploder, is prepared by a known process of granulation. It is then passed 2 over a positive electrode in a closed vessel at EHT (20,000-30,000 V) and very low current (50-120 milliamps) at 1.5-2.0 litres per minute to remove the electrons and render the surface of the microparticle positively charged 3.

To the "primed" microparticle 3 is then added 4 micronised and microfine grade inert particulate medium 5, such as magnesium stearate, which has been rendered negatively charged by passing 6 over a negative electrode in a closed vessel at EHT (20,000-30,000 V), very low current (50-120 milliamps) and 1.5-2.0 litres per minute. The negatively charged inert particulate medium 7 is allowed to form a microscopic coat 5 around the positively charged particle of the first active agent.

Microparticles of a second active agent 8 such as tetracycline, and of a third active agent 9, for example metronidazole, are each prepared in the same manner using the same or different inert particulate medium and the three coated, active agents are ultimately mixed together 10 in the required proportions, for example 100 mg bismuth, 200 mg tetracycline HCl and 200 mg metronidazole. The molecular layer or coat of the inert particulate medium insulates the active agents from each other and so prevents them from cross-reacting and forming toxic or unwanted by-products. The mixed microparticles are blended with binders, fillers and disintegrants/exploders as above and the whole mixture can be then compressed into a tablet 11 which contains the correct dosage of each active agent in a honeycombed or web-like matrix represented in part in Figure 1 by three microparticulate cells of, for example, coated bismuth subsalicylate 3, tetracycline 8 and metronidazole 9, respectively.

The microparticles which are to be electrostatically coated are preferably milled and sieved to a granular mass of uniform particle size which, according to the compound used, may range from 10-150 μm . It is also preferable that the microparticles or microgranules are subjected to complete drying in a fluid bed dryer and to intense high energy movement or flow in the dryer both before and after milling and sieving. This enhances the acceptance of an electrical charge in the priming

process that follows as the high energy and dry, hot friction will render the microparticles more adaptable to the electrical change.

The inert particulate medium for electrostatically coating the active components is desirably any inert material that acts both as a lubricant and a protective agent eg. one or more of magnesium stearate or silicon dioxide or the like. A micronised and microfine grade medium is preferred.

Auxiliaries such as binders, fillers or disintegrant/exploder which may be included are preferably selected from polyvinyl pyrrolidone, microcrystalline cellulose, lactose granules, Crospovidone XL, Explotab (sodium starch glycolate) or Croscarmellose sodium (sodium cellulose glycolate) or the like.

Each individual active component can vary from 2 to 500 mg. Bismuth compounds suitable in the present invention include those selected from the group consisting of bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, bismuth citrate, tripotassium dicitrato bismuthate, bismuth subgallate, bismuth subnitrate, bismuth tartrate, bismuth salicylate, bismuth subsalicylate, and mixtures thereof are preferred bismuth salts for use in this invention. A variety of bismuth containing compositions are available commercially including, for example, DeNol, containing tripotassium dicitrato bismuthate (sold by Gist-Brocades N.V.), Noralac, containing bismuth aluminate, alginic acid, and magnesium carbonate (manufactured by North American Pharmaceuticals), Roter bismuth, containing bismuth subnitrate (sold by Roter Laboratories), Fensobar Polvo, containing bismuth subcarbonate among other materials (manufactured by USV Pharmaceutical Corporation), and Pepto-Bismol, containing bismuth subsalicylate (sold by The Procter & Gamble Company). The lower dosage of bismuth contemplated by the invention may range from 20-200 mg per tablet, preferably 100 mg.

Preferably, the antibiotic or antibacterial agent may be selected from one or more of tetracyclines, penicillins, quinolones, cephalosporins, furazolidones, lincosamides, nitrofurantoin, nitromidazoles, macrolides and/or polypeptides.

Preferably, the second antibiotic or antibacterial agent is selected from one or more of quinolones, furazolidones, nitrofurantoin, and/or metronidazoles.

More preferably the first antibiotic or antibacterial agent is selected from tetracyclines and/or penicillins and the second antibiotic or antibacterial agent is a metronidazole. The first and second antibiotics or antibacterial agents are not the same, although they may be selected from the same class.

The tetracyclines include tetracycline, oxytetracycline, doxycycline, demeclocycline, methacycline and minocycline.

The penicillins include penicillin G, penicillin V, oxacillin, nafcillin, ampicillin, amoxicillin, cloxacillin and carbenicillin.

The nitronidazoles include metronidazole and tinidazole.

Rifampin, trimethoprim and/or nalidixic acid may also be used.

The cephalosporins include cephalexin, cefaclor, cephapirin, cephradine and cefadroxil as well as second and third generation cephalosporins.

The polypeptide antibiotics include polymyxin B, bacitracin, colistin sulfate and/or spectinomycin HCl.

The macrolides include erythromycin, clarithromycin, azithromycin, and roxithromycin.

Quinolones include ciprofloxacin, norfloxacin and ofloxacin.

Lincosamides include lincomycin and clindamycin.

Preferably a combination of antibiotics is employed. For example the dosage range of the antibiotics may be 20-300 mg eg. 20-250 mg per capsule/tablet tetracycline HCl and 50-300 mg of metronidazole.

When tetracycline HCl is used eg. in a tablet, it may be desirable to also incorporate a small amount of EDTA and/or vitamin E powder (d-alpha-tocopherol acid succinate). The preferred range of EDTA is 0.01-0.05% by weight of the tablet whilst that of vitamin E is 0.01%-2.0% by weight of the tablet EDTA is a chelating agent which scours stray metal ions to form insoluble, inert and innocuous complexes and further prevents undesirable degradation of the active components. The addition of vitamin E also helps to prevent oxidation.

Preferably the treatment is combined with the administration of an acid suppressant such as a histamine₂ antagonist such as cimetidine, ranitidine or famotidine to effect symptomatic relief and ulcer epithelialization. Other acid suppressants may

be used instead of a histamine₂ antagonist such as benzimidazole or prostaglandins. Alternatively, the histamine₂ blocker, proton pump inhibitor or other acid suppressant can be combined with the pharmaceutical composition of the present invention.

In a preferred aspect of the invention, the dose unit may additionally comprise a microencapsulated proton-pump inhibitor such as omeprazole, lansoprazole, pantoprazole or the like. The dosage may be 2-40 mg, preferably 10 mg per tablet. The microencapsulation prevents cross-reaction between the inhibitor and the three active agents. The proton pump inhibitor potentiates eradication of *H. pylori* by acid reduction, antibiotic activation and direct inhibition of proton pumps in the bacteria.

During the manufacture of the dose unit, it is preferable that exposure of all the components to oxygen is kept to a minimum. This can be achieved by tableting and mixing the components under a blanket of nitrogen. The resulting dose unit can be further protected from oxygen, humidity, heat and hence degradation and/or inactivation by being individually packaged in blister packs, preferably in a nitrogen gas atmosphere, thus creating a negative oxygen gradient outside each tablet.

The active components which may be combined in dose units in accordance with the invention are preferably selected from the group comprising: a) bismuth, tetracycline and metronidazole, b) bismuth, amoxycillin, metronidazole or tinidazole, c) bismuth, tetracycline and azithromycin, d) a macrolide, proton pump inhibitor and a nitromidazole such as:

- i) clarithromycin, omeprazole and tinidazole or
- ii) clarithromycin, omeprazole and metronidazole.

Dose units in accordance with the invention may contain two or more of the active agents herein described or two or more agents for treating other diseases. It is also possible to co-administer the dose units with separate, known units or capsules containing other drugs eg. proton pump inhibitors. The dose units may be administered once daily through to five times daily and can be taken between two and twenty-eight days. The invention may be embodied in various other forms in a manner known and understood by those skilled in the art.

The invention, by enabling normally cross-reactive components of a therapeutic regimen to be combined safely into a single unit provides clinically acceptable, stable and efficacious medication.

The combination of the three components of "Triple Therapy" in a single unit allows not only for the delivery of a considerably lower dose and bulk volume but has also maintained eradication of about 90% of *H. pylori*.

The unique, electrostatic bonding of inert medium to each drug provides a microscopic layer of skin or coat which contributes minimally to the "dead" or "empty" spaces between each drug when mixed into a dose unit such as a tablet. This allows a unit of smaller and desirable size to be produced and also enables the active components to be uniformly combined with virtually no interaction or cross-reaction. Upon ingestion of the tablet, the intercellular exploders ensure the prompt disintegration of the tablet and dispersion of the encapsulated and insulated active agents. The intracellular exploders blended with each agent then ensures its dispersion from the micronised, insulating coat.

The combination therapy dose units contemplated herein may be used for the treatment of *Helicobacter* infection in animals as well as man. The infections may be related to various disease states associated with *H. pylori* eg. gastroduodenal ulcers, non-ulcer dyspepsia, reflux symptoms, mucosa associated lymphoid tissue lymphoma (MALT-lymphoma), gastric mucosal atrophy, intestinal metaplasia, dysplasia, carcinoma, reflux oesophagitis and gastritis. Asymptomatic carriers of the infection may also be treated with the dose unit.

Although the present invention has been described in terms of preferred embodiments it will be evident to those skilled in the art that variations and modifications are possible whilst not departing from the basic principles and the spirit of this invention.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of preventing interaction between a plurality of active agents at risk of interacting in a combination therapy dose unit, said method comprising the steps of:
 - (i) charging particles of a first active agent,
 - (ii) charging particles of an inert particulate medium with a charge of opposite polarity to that of the charged particles of the first active agent,
 - (iii) allowing the charged inert particulate medium particles to electrostatically adhere to the charged particles of the first active agent thereby to coat the active agent with inert particulate medium; and
 - (iv) combining the coated first active agent particles with other active agents of the dose unit.
2. A method according to claim 1, further comprising the steps of:
 - (i) charging particles of a second active agent,
 - (ii) charging particles of the same or a different inert medium with a charge of opposite polarity to that of the charged particles of the second active agent,
 - (iii) allowing the charged inert particulate medium particles to electrostatically adhere to the charged particles of the second active agent; and
 - (iv) combining the coated second active agent with the coated first active agent.
3. A method according to any one of the preceding claims, wherein the active agents are a bismuth compound and at least an antibiotic or antibacterial substance.
4. A method according to claim 3, wherein the bismuth compound is selected from bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, colloidal bismuth subcitrate, bismuth citrate, tripotassium dicitrate bismuthate, bismuth subgallate, bismuth subnitrate, bismuth tartrate, bismuth salicylate, bismuth subsalicylate or combinations thereof.
5. A method according to any one of the preceding claims, wherein the antibiotic or antibacterial agent is selected from one or more of tetracyclines, penicillins, quinolones, cephalosporins, furazolidones, lincosamides, nitrofurantoin, nitromidazoles, macrolides and/or polypeptides.

6. A method according to claim 5, wherein the antibiotic is tetracycline, metronidazole or a combination thereof.
7. A method according to any one of the preceding claims, wherein the combination therapy dose unit further comprises an acid suppressant.
8. A method of claim 8, wherein the acid suppressant is electrostatically bonded to an inert particulate medium according to the method of claim 1.
9. A method of claim 7 or claim 8, wherein the acid suppressant is a histamine antagonist.
10. A method according to claim 9, wherein the histamine antagonist is selected from cimetidine, ranitidine, famotidine, nazatidine or prostaglandins.
11. A method according to claim 7 or claim 8, wherein the acid suppressant is a proton pump inhibitor.
12. A method according to claim 11, wherein the proton pump inhibitor is selected from omeprazole, lansoprazole or pantoprazole
13. A method according to any one of the preceding claims, wherein the inert particulate medium is magnesium stearate or silicon dioxide.
14. A method according to any one of the preceding claims, wherein the coating of the active agent with inert particulate medium is performed under a blanket of nitrogen.
15. A method of any one of the preceding claims further comprising the step of combining the particles of at least one active agent coated with the inert particulate medium into a tablet.
16. A combination therapy dose unit comprising at least one active agent which has been coated with an inert particulate medium according to the method of claim 1.
17. A combination therapy dose unit according to claim 16, further comprising a proton pump inhibitor.
18. A combination therapy dose unit according to claim 16 or claim 17, wherein the dose unit comprises one of the following combinations:
 - a) bismuth, tetracycline and metronidazole;
 - b) bismuth, amoxycillin, metronidazole or tinidazole;
 - c) bismuth, tetracycline and azithromycin; or

d) a macrolide, proton pump inhibitor and a nitromidazole combination consisting of:

- i) clarithromycin, omeprazole and tinidazole or
- ii) clarithromycin, omeprazole and metronidazole.

19. A combination therapy dose unit according to any one of claims 16 to 18 wherein each individual active agent is present in an amount from 2mg to 500mg.

20. A combination therapy dose unit according to any one of claims 16 to 19, comprising 100 mg bismuth, 200 mg tetracyclin and 200 mg metronidazole.

21. A combination therapy dose unit according to anyone of claims 16 to 20, comprising a proton pump inhibitor in the amount of between 2mg and 40mg.

22. A combination therapy dose unit according to any one of claims 16 to 21, further comprising EDTA and/or vitamin E.

23. A combination therapy dose unit according to any one of claims 16 to 22, in the form of a tablet.

24. A combination therapy dose unit according to any one of claims 16 to 23 wherein the dose units are individually packaged in blister packs.

25. A method of preventing or treating a disorder in a host requiring administration of a plurality of active agents, comprising the administration of a combination therapy dose unit according to any one of claims 16 to 24.

26. A method according to claim 25, further comprising co-administration of separate dose units comprising other active agents.

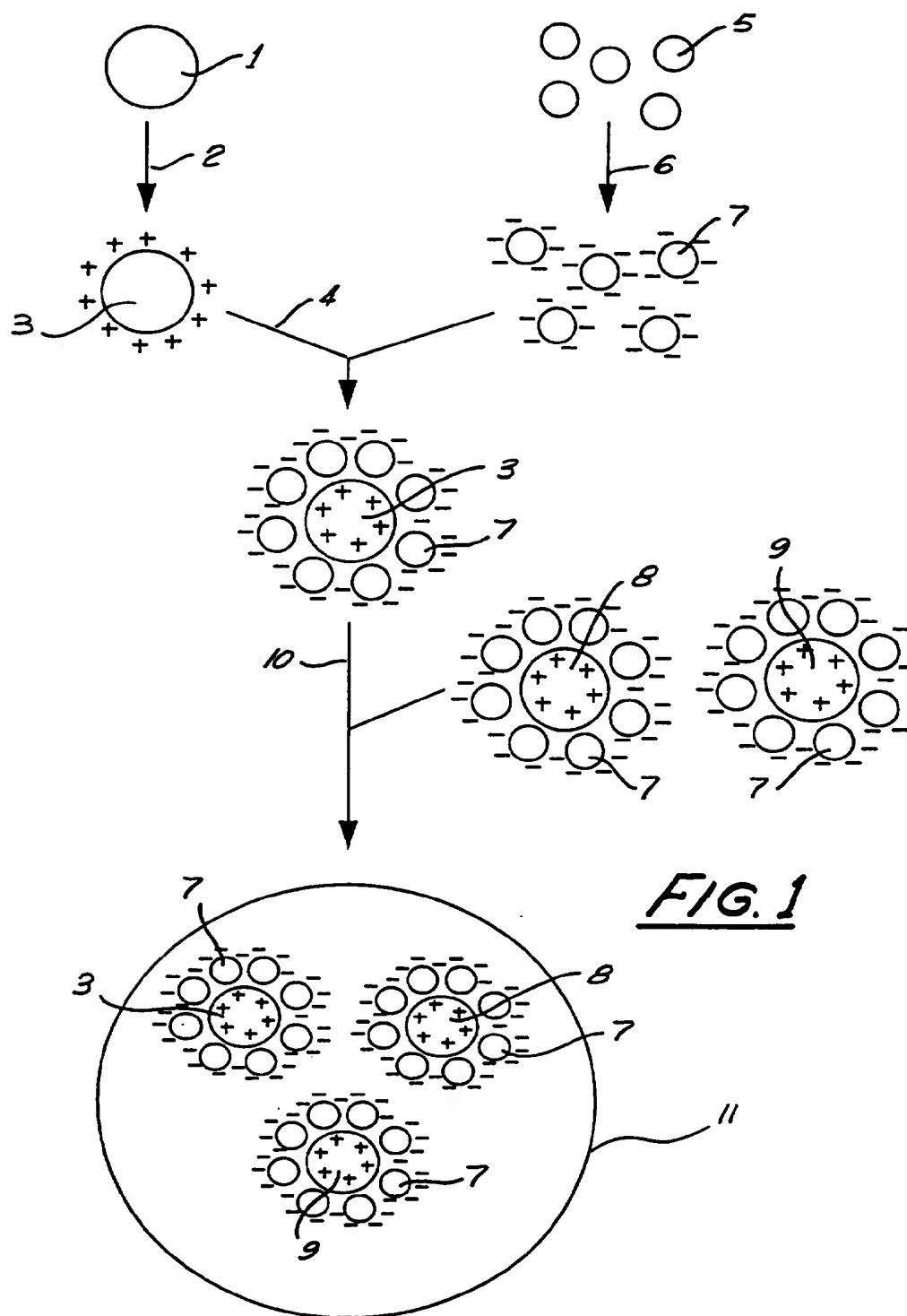
27. A method according to claim 25 or claim 26, wherein the disorder is a gastrointestinal disorder.

28. A method according to any one of claims 25 to 27, wherein the disorder is due to or associated with an infection with *Helicobacter.pylori*.

29. A method of preventing interaction between two active agents, substantially as hereinbefore described with reference to any one of the Examples.

30. A combination therapy dose unit, substantially as hereinbefore described with reference to any one of the Examples.

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**FIG. 1**

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 95/00434

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl⁶: A61K 9/20, 9/16, 31/29, 31/65, 31/415, 31/43, 31/71, 31/44, B01J 13/10, A61J 3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC : A61K, A61J 3/00, B01J 13/10

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU : IPC as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT, JAPIO, CASM, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	AU,B, 25405/88 (623868) (BORODY) 2 May 1989 pages 3-6	
A	AU,A, 24584/92 (GLAXO GROUP LIMITED) 25 March 1993 pages 3-4	
A	AU,A, 12472/92 (THE PROCTER & GAMBLE COMPANY) 17 August 1992 entire document	

☒ Further documents are listed in the continuation of Box C

☐ See patent family annex

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Date of the actual completion of the international search
25 September 1995

Date of mailing of the international search report

24 OCTOBER 1995

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/AU 95/00434

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	AU,B, 65467/69 (449567) (BAYER AKTIENGESELLSCHAFT) 24 June 1971 entire document	
A	GB,A, 2128350 (CANON KABUSHIKI KAISHA) 26 April 1984 page 6, line 6-10	
A	GB,A, 2061983 (SINLOIHI COMPANY LIMITED) 20 May 1981 page 1, line 5-8	
A	GB,A, 2029425 (SINLOIHI COMPANY LIMITED) 19 March 1980 page 1, line 35-43	

Information on patent family members

PCT/AU 95/00434

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AU	24584/92	CA GB	2078579 2259647	EP JP	533281 6092850	FR	2682040
AU	12472/92	US	5192752	WO	9211848		
GB	2128350	DE US	3332621 4565764	GB	2128350	JP	59048771
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GB	2029425	CA GB	1124916 2029425	DE JP	2927249 55009632	FR US	2430427 4314932
END OF ANNEX							

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 401/12	A1	(11) International Publication Number: WO 96/16959 (43) International Publication Date: 6 June 1996 (06.06.96)
(21) International Application Number: PCT/SE95/01414 (22) International Filing Date: 27 November 1995 (27.11.95) (30) Priority Data: 9404192-8 2 December 1994 (02.12.94) SE (71) Applicant: ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventor: BRÄNDSTRÖM, Arne; Karlsborg 5, S-271 Ystad (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		(81) Designated States: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

(54) Title: A PROCESS FOR THE PREPARATION OF BENZIMIDAZOLE DERIVATIVES**(57) Abstract**

A new process for the preparation of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate and the single enantiomers thereof which compounds by administration inhibit exogenously or endogenously stimulated gastric acid secretion.

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A PROCESS FOR THE PREPARATION OF BENZIMIDAZOLE DERIVATIVES

DESCRIPTION

Field of the invention

The object of the present invention is to provide a process for the preparation of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate and its single enantiomers which compounds by administration inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of peptic ulcer.

It is a specific primary object of the invention to provide a process which makes it possible to isolate the pure 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate or its single enantiomers, hereinafter called the 5-isomer which includes its single enantiomers, i.e. the (+)-5-isomer and (-)-5-isomer respectively. The compounds are separated from an isomeric mixture of the 5-isomer and 6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate or its single enantiomers, the latter hereinafter called the 6-isomer which includes its single enantiomers.

Prior art and background of the invention

Benzimidazole compounds have in its 5-membered ring two nitrogen atoms of which only one can have a substituent. The nitrogens in the 5-membered ring are not equivalent if the 6-membered ring is asymmetrically substituted. Thus, different isomers will arise depending on which of the two inequivalent nitrogens is bearing the substituent. These isomers have different properties. For example the 5-isomer shows a higher chemical stability in the solid state making the compound useful in the preparation of pharmaceutical formulations. Therefore it is desirable to isolate the pure 5-isomer from an isomeric mixture of the 5- and 6-isomers. These compounds also show high bioavailability and exhibits a high chemical stability in solution also at acidic pH which make the compound useful for non-enteric coated formulations.

The isomeric mixture of the 5- and 6-isomer is disclosed in PCT/SE91/00415. It is believed that the 5-isomer and the 6-isomer are metabolized into the corresponding compounds carrying H in the N-1 position before exerting their effect. These corresponding compounds are disclosed in PCT/SE91/00416.

Processes to prepare the desired 5-isomer have been tried where the starting compound being a 5-isomer which has a substituent on one of the nitrogen atoms and which can be transformed into the desired nitrogen substituent. However it is difficult to prepare the pure isomers by applying the above mentioned strategy.

Another process tried is to synthesize the sulphide having the desired substituent on one of the nitrogen atoms and by oxidation transfer the sulphide into the desired sulfoxide. The starting compound in these processes could be either in the form of its 5-isomer or the isomeric mixture. When mixtures of structural isomers are

obtained in any of the above processes, the 5-isomer is isolated by means of crystallisation or chromatography.

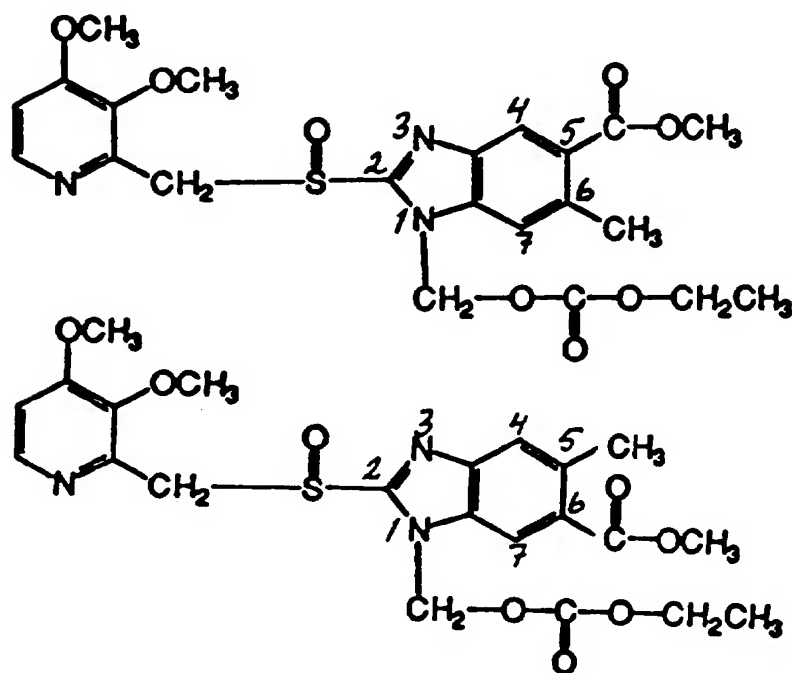
Furthermore, attempts to directly synthesize the pure 5-isomer have not succeeded and attempts to isolate the 5-isomer from an isomeric mixture by recrystallisation or chromatography in various solvents have resulted in poor yields.

A preparative method for use of attack at the 2-position of benzimidazole has been described previously (D.R. Graber, R.A. Morge, J.C. Sih, J. Org. Chem. 1987, 52, 4620-4622). The present application describes a novel and efficient way to obtain the pure 5-isomer.

Outline of the invention

It has now surprisingly been found that by using the difference in chemical reactivity of the 5-isomer (including the single enantiomers thereof) and the 6-isomer (including the single enantiomers thereof) it is possible to isolate the 5-isomer easily. N-substituted benzimidazoles are susceptible to nucleophilic attack on the carbon in the 2-position, and here the 5- and 6-positions can show a high difference in chemical reactivity. This rate difference for a pair of isomers is influenced by solvent characteristics, characteristics of the nucleophile, and the substituent pattern and position of the substituents of the respective isomers. High isomer selectivity in the nucleophilic attack in the 2-position is favoured by electron with-drawing groups in the benzimidazole and by using dipolar aprotic solvents.

Thus, the present invention provides a process for the preparation of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate and the single enantiomers thereof by reacting an isomeric mixture of two compounds of the formula I or of the formula Ia or Ib



Ia (+)-enantiomers

Ib (-)-enantiomers

with a suitable nucleophile in a solvent. Preferred nucleophiles are compounds having the formula II



wherein R is a straight or branched, substituted or unsubstituted alkyl $\text{C}_1\text{-C}_{12}$, preferably a lower alkyl $\text{C}_1\text{-C}_5$ unsubstituted or substituted with a hydroxy, carboxy, amino and/or amido group, or R is a substituted or unsubstituted aryl group, preferably a phenyl.

The reaction is yielding the 5-isomer and degradation products from the 6-isomer and from some 5-isomer.

The 6-isomer has a higher rate of chemical reactivity than the 5-isomer and it is thus possible to selectively degrade the 6-isomer in the mixture. Subsequently, the 5-isomer is isolated from the reaction mixture by conventional work-up procedures.

Preferably the reaction is performed in the presence of a base, such as a bicarbonate.

Preferably the solvent is a dipolar aprotic solvent, such as dimethylsulphoxide (DMSO).

Preferably the nucleophile is thiophenol sodium salt, propanethiol sodium salt, ethanethiol sodium salt, n-butylmercaptane, t-butylmercaptane,

2-mercaptoethanol, 1-pentanemercaptane, p-thiocresol, (3,4-dimethoxy-2-pyridinyl)methylthiol or N-acetylcysteine. The most preferred nucleophiles are t-butylmercaptane and 2-mercaptoethanol.

The nucleophile can be added to the reaction either as a salt or as a neutral compound.

The reaction may be performed at temperatures ranging from 0° to 40° C and has been found to be fast at room temperature.

The invention is illustrated by the following examples.

Example 1. Preparation of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate using t-butylmercaptane as nucleophilic agent

Grinded potassium hydrogen carbonate (1.5 g, 15.0 mmol) and a 73:27-mixture of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate (3.0 g, 6.0 mmol) were dissolved and suspended, respectively, in DMSO (20 mL) under argon and stirring at room temperature. t-Butylmercaptane (0.3 mL, 2.67 mmol) was added drop-wise with a syringe. The reaction mixture was stirred under argon for 3 hours and then diluted with dichloromethane (50 mL; exothermic) and extracted with water (3*25 mL) to remove DMSO, hydrophilic products and inorganic materials. The combined water phases were extracted with dichloromethane (25 mL). The combined organic phases were dried with anhydrous sodium sulphate, filtered, and evaporated in vacuo to give a yellow

syrup. Crystallisation from hot isopropanol (20 mL) gave almost colourless, needle-shaped, micro-crystals which were washed with a little isopropanol (2*2 mL). Yield: 1,64 g (purity 96%; isomer ratio 98:2).

Example 2. Preparation of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate using 2-mercaptoethanol as nucleophilic agent

Grinded potassium hydrogen carbonate (1.5 g, 15.0 mmol) and a 73:27-mixture of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate (3.0 g, 6.0 mmol) were dissolved and suspended, respectively, in DMSO (20 mL) under argon and stirring at room temperature.

2-Mercaptoethanol (0.2 mL, 2.85 mmol) was added drop-wise with a syringe. The reaction mixture was stirred under argon for 10.5 hours and then diluted with dichloromethane (50 mL) and extracted with water (3*25 mL) to remove DMSO, hydrophilic products and inorganic materials. The combined water phases were extracted with dichloromethane (25 mL). The combined organic phases were dried with anhydrous sodium sulphate, filtered, and evaporated in vacuo to give a yellow syrup. Crystallisation from hot ethanol (99.5%; 20 mL) gave almost colourless, needle-shaped, micro-crystals which were washed with a little ethanol (99.5%; 3*2 mL). Yield: 1,29 g (purity 96%; isomer ratio 98:2).

Example 3. Enrichment of 5-isomer in pilot scale

DMSO (140 L) and a 70:30-mixture of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate (54 kg, 29.3 mol) were added to a 1000-litre reactor at 18 °C to afford an almost clear solution to which potassium hydrogen carbonate (2.0 kg, 20 mol) was added. t-Butylmercaptane (1.69 L, 14.9 mol) was then added under vigorous stirring. A sample was taken after 50 minutes analysed for isomer composition which was found to be 90:10. Additional t-butylmercaptane (0.3 L, 3.55 mol) was added, the reaction mixture was stirred for additional 45 minutes before a new sample was taken and analysed for isomer composition which was found to be 96:4. The achieved isomer ratio was regarded as satisfactory. Dichloromethane (200 kg/20 min; exothermic reaction) and water (112 kg/5 min) was added and the resulting mixture was first stirred for 20 minutes and then left without stirring for 30 minutes. The water phase was removed and additional water (75 kg) was added and the resulting mixture was first stirred for 15 minutes and then left without stirring for 25 minutes. The water phase was removed and the organic phase was evaporated in vacuo (jacket temperature 30 °C) to give a butter-like residue. Ethanol (104 kg) was added to facilitate removal of residual dichloromethane by evaporation in vacuo (jacket temperature was raised to 50 °C) which continued until a clear solution had been achieved. The clear solution was stirred at approximately 55 °C for approximately 45 minutes and then cooled (cooling rate 50 °C/h). When the temperature of the solution reached 40 °C, water (65 kg) was added under vigorous stirring. When the temperature reached 35 °C, 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate (4.5 g) was added to induce

crystallisation. Crystallisation started 15 minutes later at which time stirring was reduced from vigorous to gentle. The resulting slurry of crystals was filtered after 11 hours of gentle stirring at 20 °C. The filter-cake was washed with a water:ethanol mixture (1:3; 2*20 L) and dried to give 16.3 kg off-white crystals (water content 33%; ethanol content 11%; purity by HPLC 97.7%; isomer ratio 97:3).

Example 4. One-pot reaction: synthesis of isomer mixture and enrichment of 5-isomer

Potassium carbonate (156 mg, 1.1 mmol) and 18-crown-6 (60 mg, 0.23 mmol) was added to DMSO (7 mL) under stirring. Then, 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole (400 mg, 0.8 mmol; water content 3.7%; purity 96.7%). When a solution had been achieved after approximately 50 minutes, chloromethyl ethyl carbonate (171 mg, 1.23 mmol) was added. Stirring was continued for 18 hours to afford a clear, dark-yellow, liquid phase and some white particles. Analysis of a sample by HPLC indicated a 94% yield of a 61:39-mixture of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate. Then, t-butylmercaptane (50 µL, 0.46 mmol) was added and allowed to react for 40 minutes before a sample was withdrawn and analysed by HPLC, which indicated that a 74:26 isomer ratio had been achieved. Additional t-butylmercaptane (50 µL, 0.46 mmol) was added and allowed to react for 30 minutes before another sample was withdrawn and analysed by HPLC, which indicated that the isomer ratio had changed to 99:1. The reaction mixture was then diluted with dichloromethane

(3 mL) and extracted with water (3*2 mL) to remove DMSO, hydrophilic products and inorganic materials. The organic phase was evaporated in vacuo to give a syrup. Crystallisation from hot ethanol (99.5%; 5 mL) gave yellowish micro-crystals. Yield: 117 mg (purity 84%; isomer ratio 99:1).

Example 5. Preparation of (-)-5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)-sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate

A mixture of two regio isomers (0.85 g, 1.73 mmol), namely a mixture of (-)-5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate ($\approx 60\%$) and (-)-6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate was mixed with potassium hydrogen carbonate (83 mg, 0.83 mmol) and acetonitrile. A dropwise addition of 2-mercaptoethanol (0.12 ml, 1.7 mmol) was followed by stirring at room temperature for one hour. The mixture was evaporated and the residue partitioned between methylene chloride and water. The organic layer was dried over Na_2SO_4 and then evaporated. The oily residue was purified by flash chromatography on silica gel with a mixture of methanol (2-4%) and ammonia saturated methylene chloride as eluent. The product was triturated with ethanol, to give the title compound (0.15 g, 44%) in the form of a white solid, mp. 144-147°C, $[\alpha]_D = -120.8^\circ$ ($c = 1.0\%$, chloroform).

Example 6. Preparation of (+)-5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)-sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate

A mixture of two regio isomers (0.62 g, 1.26 mmol), namely a mixture of (+)-5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)-sulfinyl)-1H-

benzimidazole-1-ylmethyl ethyl carbonate ($\approx 65\%$) and (+)-6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate was mixed with potassium hydrogen carbonate (45 mg, 0.45 mmol) and acetonitrile. A dropwise addition of 2-mercaptoethanol (0.07 ml, 1.0 mmol) was followed by stirring at room temperature for one hour. The mixture was evaporated and the residue partitioned between methylene chloride and water. The organic layer was dried over Na_2SO_4 and then evaporated. The oily residue was purified by flash chromatography on silica gel with acetonitrile as eluent. The product was triturated with ethanol, to give the title compound (0.23 g, 44%) in the form of a white solid, mp. $145-147^\circ\text{C}$, $[\alpha]_D = +122.7^\circ$ ($c = 1.0\%$, chloroform).

Preparation of intermediates

Example 7. Preparation of (+)-5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole

The crude product of the diastereomers of a mixture of two regioisomeric mandelic esters, namely 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)-(R/S)-sulfinyl)-1-((R)-mandeloyloxymethyl)-1H-benzimidazole and 6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)-(R/S)-sulfinyl)-1-((R)-mandeloyloxymethyl)-1H-benzimidazole (1.8 g, 3.3 mmol) was divided into three parts. Each part was chromatographed on a reversed phase column (HPLC, Kromasil C8) in order to separate the diastereomers. The stereoisomers were easily separated by elution with a mixture of aqueous 0.1 M ammonium acetate and acetonitrile (70/30), but each separated diastereomer consisted of a mixture of the two regioisomers. These intermediates were used directly in their solutions during the hydrolyses; To the acetonitrile/aqueous solutions of the more lipophilic

diastereomer were added 1 M aqueous solutions of NaOH until the pH was around 12-13. After 5 minutes the solutions were neutralised with 3.0 M aqueous solutions of NH₄Cl. The solutions from each preparation were combined and extracted with methylene chloride whereupon the organic phases were dried over Na₂SO₄. Removal of the solvents and flash chromatography of the residue (silica gel, methanol-methylene chloride gradient 1-8%) yielded 250 mg of a yellow oil. The product was crystallised by adding acetonitrile (3 ml) and after filtration there was obtained 210 mg (32%) of the title compound as white crystals m.p. 171-173° C. $[\alpha]^{20}_D = +153.1^\circ$ (c=0.5%, chloroform).

Example 8. Preparation of (-)-5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole

To the acetonitrile/aqueous solutions of the less lipophilic diastereomer of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)-(R/S)-sulfinyl)-1-((R)-mandeloyloxymethyl)-1H-benzimidazole and 6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)-(R/S)-sulfinyl)-1-((R)-mandeloyloxymethyl)-1H-benzimidazole (obtained from the very same reversed phase chromatographic preparations described in Example 7) were added 1.0 M NaOH until the pH was around 12-13. After 5 minutes the solutions were neutralised with 3.0 M aqueous solutions of NH₄Cl. The solutions from each preparation were combined and extracted with methylene chloride whereupon the organic phases were dried over Na₂SO₄. Removal of the solvents and flash chromatography of the residue (silica gel, methanol-methylene chloride gradient 1-8%) yielded 270 mg of a yellow oil. The product was crystallised by adding acetonitrile (3 ml) and after filtration there was obtained 210 mg (32%) of the title compound as white crystals m.p. 173-174° C. $[\alpha]^{20}_D = -150.0^\circ$ (c=0.5%, chloroform).

Example 9. Preparation of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)-(R/S)-sulfinyl)-1-(R)-mandeloyloxymethyl)-1-H-benzimidazole and 6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)-(R/S)-sulfinyl)-1-(R)-mandeloyloxymethyl)-1H-benzimidazole

A solution of 0.33 g (8.2 mmol) sodium hydroxide in 1.6 ml water was added to a mixture of 1.4 g (4.1 mmol) tetrabutylammonium hydrogen sulphate and 0.62 g (4.1 mmol) of (R)-(-)-mandelic acid. Chloroform (50 ml) and a mixture of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1-(chloromethyl)-1H-benzimidazole and 6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1-(chloromethyl)-1H-benzimidazole (as racemates) were added and the mixture was refluxed for 3 hours. The reaction mixture was chilled and then partitioned between ethyl acetate and water. The layers were separated and the organic phase was washed with water and dried over Na₂SO₄. Removal of solvents yielded a diastereomeric mixture of the two regioisomeric mandelic esters. The crude product was used directly in the chromatographic step where the diastereomers were separated (Examples 7 and 8). Yield: 2.4 g, 62%.

Example 10. Synthesis of a mixture of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate

To a suspension of 0.45 g (1.1 mmol) of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole and 0.25 g (1.8 mmol) of potassium carbonate anhydrous in 45 ml of dry acetonitrile, 0.21 g (1.5 mmol) of chloromethyl ethyl carbonate dissolved in 5 ml of acetonitrile was added. The reaction mixture was stirred at room temperature over night. The solvent was then removed in vacuo and the residue was diluted with methylene chloride and water. The organic solvent was dried over anhydrous sodium sulphate. Removal of the solvent in vacuo gave the crude product, which was chromatographed with silica gel and eluted with ethyl acetate to provide 0.94 g yellow oil which slowly crystallised. Recrystallisation with ethanol yielded 0.25 g (44 %) of the isomeric mixture of the title.

Example 11. Preparation of (-)-5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate and (-)-6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate

(-)-5-Carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole (1.0 g, 2.6 mmol) was mixed with potassium carbonate (0.39 g, 2.8 mmol) and acetonitrile (40 ml). Chloromethyl ethyl carbonate (0.36 g, 2.6 mmol) was added and the mixture was stirred over night. After evaporation the residue was partitioned between water (50 ml) and methylene chloride (50 ml). The

aqueous phase was extracted with methylene chloride (50 ml) and the combined organics were dried (Na_2SO_4) and evaporated. The oily residue was triturated with ethanol, to give the title compounds as a regio isomeric mixture (0.95 g, 75 %) in the form of a white solid, $[\alpha]_D = -121.5^\circ$ ($c=0.5\%$, chloroform).

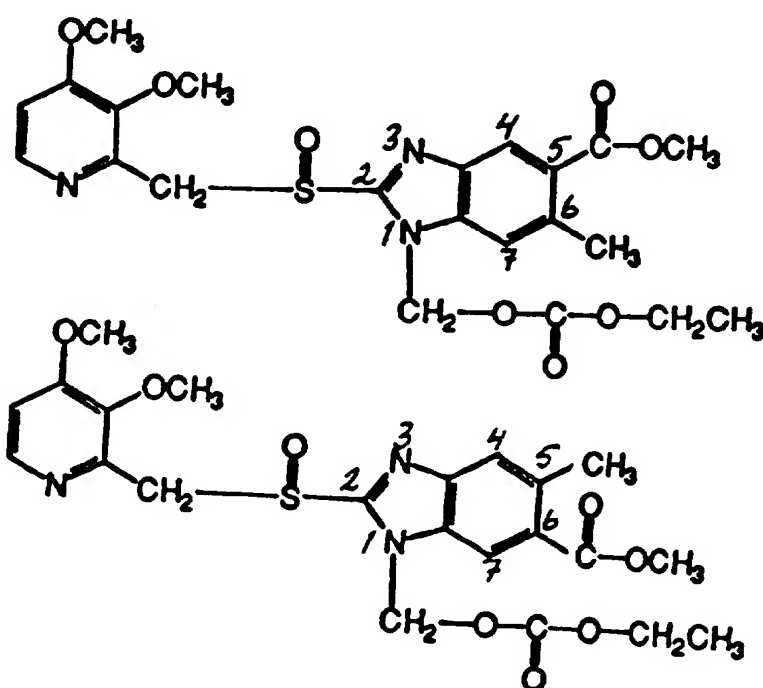
Example 12. Preparation of (+)-5-carbomethoxy-6-methyl-2-(((3,4-dimethoxypyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate and (+)-6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate

(+)-5-Carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole (0.67 g, 1.72 mmol) was mixed with potassium carbonate (0.26 g, 1.89 mmol) and acetonitrile (25 ml). Chloromethyl ethyl carbonate (0.26 g, 1.89 mmol) was added and the mixture was stirred over night. After evaporation the residue was partitioned between water (25 ml) and methylene chloride (50 ml). The aqueous phase was extracted with methylene chloride (50 ml) and the combined organics were dried (Na_2SO_4) and evaporated. The oily residue was purified by flash chromatography on silica gel, with acetonitrile/methylene chloride as eluent, to give the title compounds as a regio isomeric mixture (0.62 g, 73 %) in the form of a syrup, $[\alpha]_D = +108^\circ$ ($c=0.5\%$, chloroform).

The best way of carrying out the invention at present is according to Example 3.

CLAIMS:

1. A process for the preparation of 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate and the single enantiomers thereof characterized in that an isomeric mixture of two compounds of the formula I or of the formula Ia or Ib



Ia (+)-enantiomers

Ib (-)-enantiomers

is reacted with a nucleophile in a solvent whereby the 5-isomer is isolated from the reaction mixture.

2. A process according to claim 1, characterized in that the nucleophile having the formula II



II

wherein R is a straight or branched, substituted or unsubstituted alkyl C₁-C₁₂ or a substituted or unsubstituted aryl.

3. A process according to claim 2, characterized in that R is a straight or branched lower alkyl C₁-C₃ unsubstituted or substituted with a hydroxy, carboxy, amino and/or amido group; or a phenyl group.
4. A process according to claim 2, characterized in that the nucleophile is thiophenol sodium salt, propanethiol sodium salt, ethanethiol sodium salt, *n*-butylmercaptane, *t*-butylmercaptane, 2-mercaptoethanol, 1-pentanemercaptane, *p*-thiocresol, *N*-acetylcysteine or (3,4-dimethoxy-2-pyridinyl)methylthiol.
5. A process according to claim 4, characterized in that the nucleophile is *t*-butylmercaptane or 2-mercaptoethanol.
6. A process according to claim 1, characterized in that the solvent is a dipolar aprotic solvent.
7. A process according to claim 6, characterized in that the solvent is dimethyl sulphoxide.

8. A process according to claim 1, c h a r a c t e r i z e d in that the reaction is performed in the presence of a base.

9. A process according to claim 8, c h a r a c t e r i z e d in that the base is a bicarbonate.

10. 5-Carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate prepared by a process according to claim 1.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 95/01414

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 401/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ACTA CHEMICA SCANDINAVICA, Volume 43, 1989, Arne Brändström et al, "Chemical Reactions of Omeprazole and Omeprazole Analogues. II. Kinetics of the Reaction of Omeprazole in the Presence of 2-Mercaptoethanol" page 549 - page 568 --	1-10
A	J. ORG. CHEM., Volume 52, 1987, David R. Graber et al, "Reaction of 2-(Alkylsulfinyl)-, 2(Arylsulfinyl)-, and 2-(Aralkylsulfinyl) benzimidazoles with Thios: A Convenient Synthesis of Unsymmetrical Disulfides" page 4620 - page 4622 -- -----	1-10

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

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Date of the actual completion of the international search

6 March 1996

Date of mailing of the international search report

02 -04- 1996

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification⁶ :**A61K 9/30, 31/44, 47/18****A1**

(11) International Publication Number:

WO 96/24338

(43) International Publication Date:

15 August 1996 (15.08.96)

(21) International Application Number: PCT/SE96/00161

(22) International Filing Date: 9 February 1996 (09.02.96)

(30) Priority Data:

9500478-4

9 February 1995 (09.02.95)

SE

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Södertälje (SE).(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY,
CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS,
JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD,
MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD,
SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN,
ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent
(AZ, BY, KG, KZ, RU, TJ, TM), European patent (AT, BE,
CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT,
SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML,
MR, NE, SN, TD, TG).**Published***With international search report.*

(54) Title: NEW PHARMACEUTICAL FORMULATION AND PROCESS

(57) Abstract

A new oral pharmaceutical dosage form comprising a core material that contains a proton pump inhibitor, one or more alkaline reacting compounds and optionally pharmaceutical excipients having a water soluble separating layer and an enteric coating layer. The core material as such is alkaline reacting and the separating layer between the alkaline reacting core material and the enteric coating layer is formed in situ as a water soluble salt between the alkaline reacting compound(s) and the enteric coating polymer. The invention also describes a new efficient process for the manufacture of such a dosage form comprising two functionally different layers in one manufacturing step, and its use in medicine.

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NEW PHARMACEUTICAL FORMULATION AND PROCESS

Field of the invention

- 5 The present invention refers to new pharmaceutical formulations comprising acid labile heterocyclic compounds with gastric inhibitory effect, in the following referred to as proton pump inhibitors. The new formulations are intended for oral use. Furthermore, the present invention refers to a new method for the manufacture of such a formulation and, the use of the new formulations in medicine.

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Background of the invention

The proton pump inhibitors are for example compounds of the general formula I

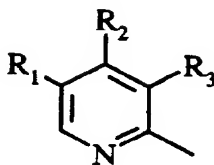
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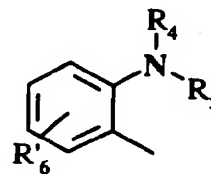
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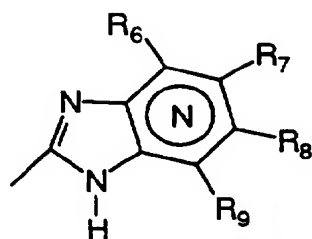


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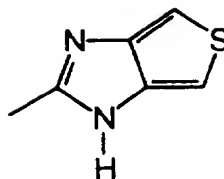


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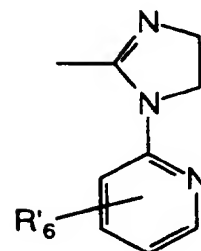
Het₂ is



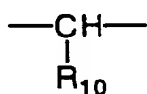
or



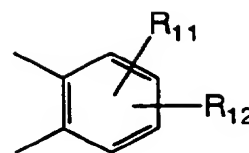
or



X =



or



5 wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R₆-R₉ optionally may be exchanged for a nitrogen atom without any substituents;

10 R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R₄ and R₅ are the same or different and selected from hydrogen, alkyl and aralkyl;

15

R'₆ is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R₆-R₉ are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxy carbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R₆-R₉ form ring structures which may be further substituted;

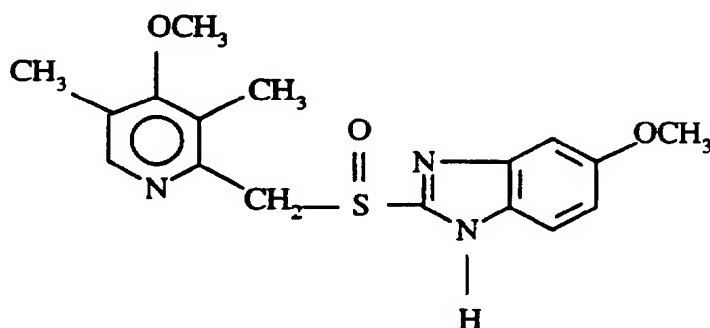
20

R₁₀ is hydrogen or forms an alkylene chain together with R₃ and

R₁₁ and R₁₂ are the same or different and selected from hydrogen, halogen or alkyl and alkyl groups, alkoxy groups and moities thereof may be branched and straight C₁-C₉ -chains or comprise cyclic alkyl groups, for example cycloalkylalkyl.

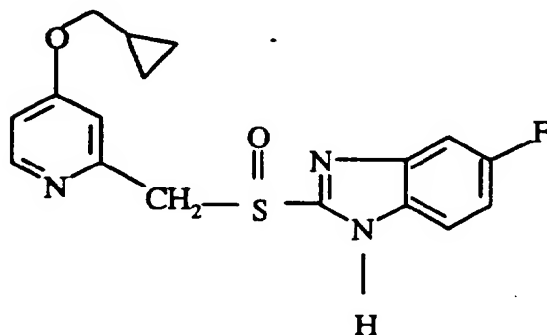
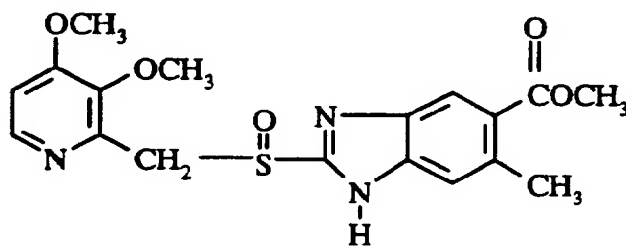
5

Examples of proton pump inhibitors according to formula I are

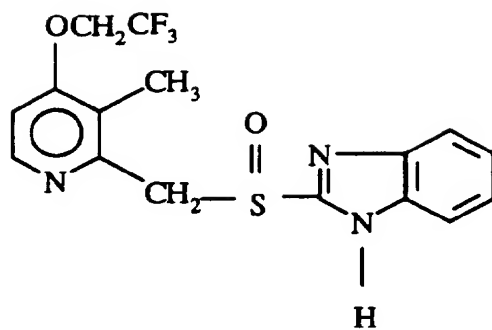


Omeprazole

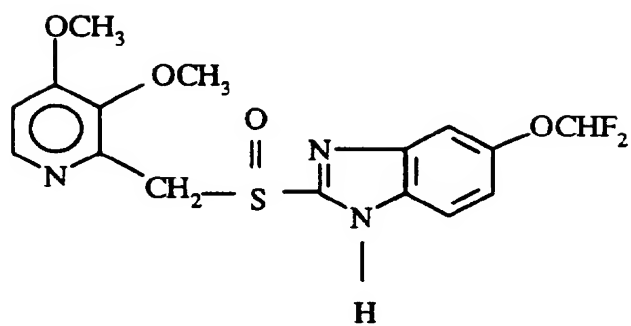
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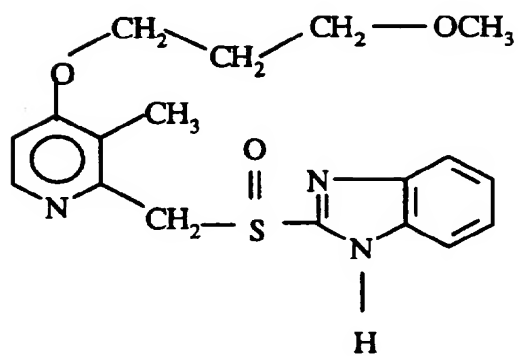


Lansoprazole



Pantoprazole

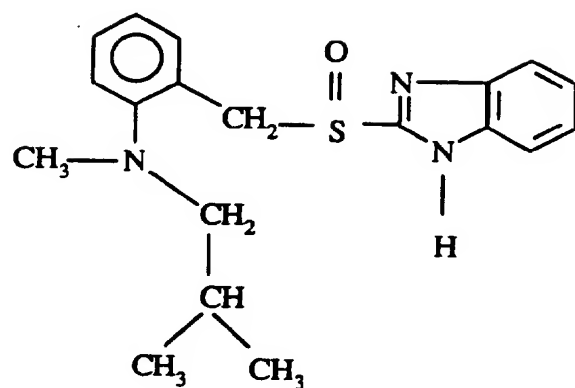
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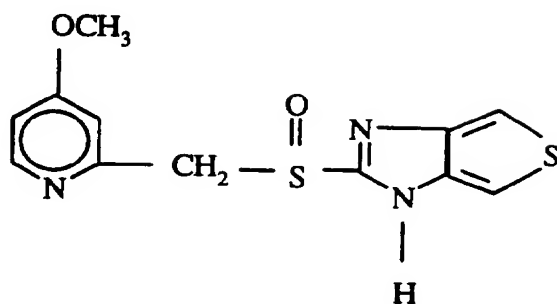
Pariprazole

10

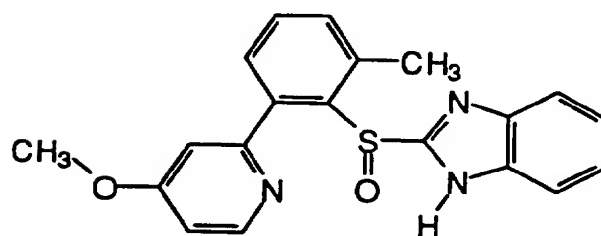
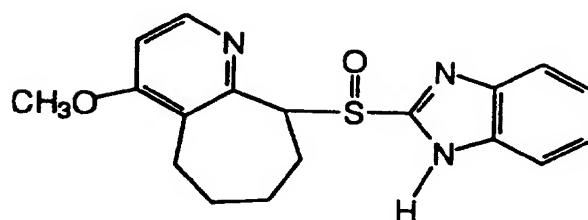
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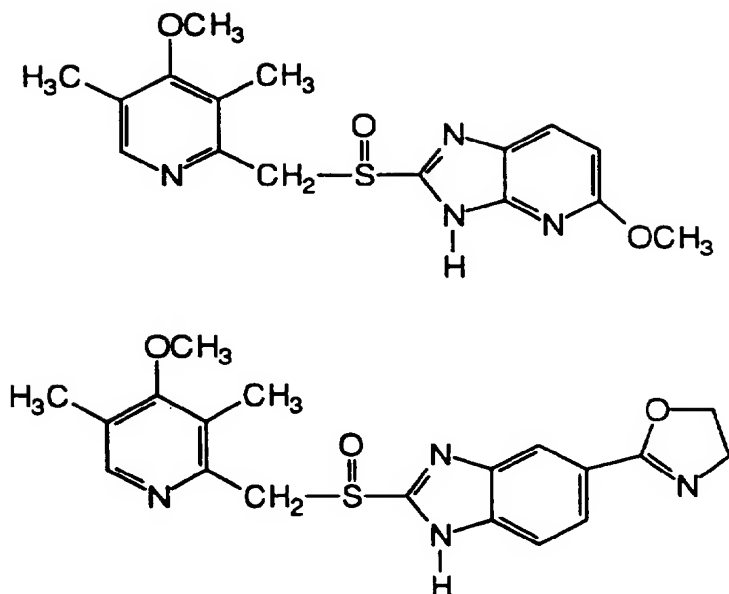


Leminoprazole



5





- 5 The proton pump inhibitors used in the dosage forms of the invention may be used in neutral form or in the form of an alkaline salt, such as for instance the Mg^{2+} , Ca^{2+} , Na^+ , K^+ or Li^+ salts, preferably the Mg^{2+} salts. Further where applicable, the compounds listed above may be used in racemic form or in the form of a substantially pure enantiomer thereof, or alkaline salts of the racemates or the single enantiomers.

10

Suitable proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO90/06925, WO91/19711, WO91/19712, and further especially suitable compounds are described in WO94/27988 and WO95/01977.

15

These proton pump inhibitors are, as already mentioned, useful for inhibiting gastric acid secretion in mammals and man. In a more general sense, they may be used for prevention and treatment of gastric-acid related diseases in mammals and man, including e.g. reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, they may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is

20

desirable e.g. in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, and in patients with gastrinomas. They may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre- and postoperatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, they may be useful in the treatment of *Helicobacter* infections and diseases related to these.

These proton pump inhibitors are, however, susceptible to degradation/transformation in acidic reacting and neutral media. The degradation is catalyzed by acidic reacting compounds and the proton pump inhibitors are usually stabilized in mixtures with alkaline reacting compounds.

In respect to the stability properties of the proton pump inhibitors mentioned above, it is obvious that a proton pump inhibitor in an oral solid dosage form must be protected from contact with the acidic reacting gastric juice and the active substance must be transferred in intact form to that part of the gastrointestinal tract where pH is less acidic, neutral or alkaline and where rapid absorption of the pharmaceutically active substance, i.e. the proton pump inhibitor, can occur.

A pharmaceutical dosage form of these proton pump inhibitors is best protected from contact with acidic gastric juice by an enteric coating layer. In US-A 4,853,230 such enteric coated preparations of different acid labile substances are described. Said preparations contain an alkaline core material comprising the active substance, a separating layer and an enteric coating layer.

Ordinary enteric coating layers, however, comprise compounds which contain acidic groups. If covered with such an enteric coating layer, the acid labile substance may rapidly decompose by direct or indirect contact with the acidic groups resulting in discoloration of the content and loss in content of the active compound with the passage of time. The discoloration can be avoided by applying some type of separating layer between the core material comprising the susceptible proton pump inhibitor and the enteric coating layer.

Thus, there are a lot of patent applications describing such a separating layer between a core material comprising the pharmaceutically active substance and an enteric coating layer. See for instance, US-A 4,786,505, EP 0,277,741 and EP 0,342,522. The prior art techniques to
5 apply at least two different layers on a pellet core or a tablet comprising an acid labile compound is rather complicated and there is a demand for finding new processes and formulations to simplify the manufacturing of such enteric coated articles comprising acid labile substances.

10 Summary of the invention.

According to one aspect of the invention a new pharmaceutical dosage form is provided in the form of an enteric coated tablet. Alternatively, individually enteric coated units are prepared and filled into a capsule, a sachet or included in a tableted multiple unit dosage
15 form.

The present invention is characterized by the presence of a separating layer between an alkaline reacting core material comprising a pharmaceutically active acid labile substance and an enteric coating layer, wherein the separating layer comprises a water soluble salt of
20 an enteric coating polymer.

According to a second aspect the present invention provides a process for the manufacture of two functionally different layers in one manufacturing step. By such a process a separating layer comprising a water soluble salt of an enteric coating polymer is obtained,
25 as well as the enteric coating layer itself.

Thus, the present invention simplifies the preparation of enteric coated articles comprising a separating layer between a core material and an enteric coating layer by providing a new process for the manufacture of such dosage forms. According to said process the separating
30 layer is formed by an in situ reaction between the enteric coating polymer and the alkaline core material comprising the pharmaceutically active substance.

Brief description of the Figures

Figure 1 is a photo showing a cross-section of a tablet manufactured according to the invention described in the present specification.

Figure 2 is a schematic drawing of the photo disclosed in Figure 1. The tablet has an enteric coating layer (3), which has been applied on an alkaline core material (1) comprising the pharmaceutically active substance. Between the enteric coating layer (3) and the core material (1) there is a separating layer (2) shown. The separating layer (2) is on the photo inked by a fluorescent colour.

Detailed description of the invention

One object of the present invention is to provide a new enteric coated pharmaceutical formulation comprising a core material that contains a proton pump inhibitor, one or more alkaline reacting compound(s) and optionally pharmaceutically acceptable excipients, which formulation has a water soluble separating layer and an enteric coating layer and wherein the core material is alkaline and the separating layer is being formed in situ during the enteric coating as a salt between the enteric coating polymer(s) and an alkaline reacting compound(s) in the core material.

Another object of the present invention is to provide a new process for the manufacture of such enteric coated pharmaceutical formulations comprising a core material of a proton pump inhibitor wherein a separating layer is formed in situ during the enteric coating by a reaction between the enteric coating polymer(s) and one or more alkaline reacting compound(s) in the core material, i.e. thereby a salt is formed between the enteric coating polymer(s) and the alkaline reacting compound(s).

The new pharmaceutical dosage form according to the invention is further characterized in the following way. Compacted tablets or individual cores (in the form of small tablets, small

beads, granules or pellets) contain the proton pump inhibitor in the form of a racemate or one of its single enantiomers or an alkaline salt of said compound or one of its single enantiomers. The tablets or individual cores, that also comprise one or more alkaline reacting compound(s) which is in the position to form a water soluble salt by a reaction with an enteric coating material, are coated with one or more enteric coating layers.

The separating layer is formed in situ by a reaction between the enteric coating polymer(s) and the alkaline reacting compound(s) in the core material during the enteric coating process.

10

The core material for the manufacture of enteric coated pellets can be prepared according to two main principles. Firstly, seeds can be layered with the proton pump inhibitor, alkaline reacting compound(s) and necessary excipients to give an alkaline reacting core material, or the alkaline reacting core material can be prepared as substantially homogeneous cores or tablets comprising the proton pump inhibitor and the alkaline reacting compound(s).

The alkaline reacting compound(s) in the core material or tablet cores, necessary for an in situ reaction with the enteric coating polymer, is a substance in the position to form a water soluble salt with an enteric coating polymer. Such alkaline reacting compounds are for instance amino acids, such as lysine, arginine, ornithine, histidine, organic buffering compounds such as trometamine (i.e. Tris-buffer), N-amino sugars such as N-methyl-D-glucamine (i.e. Meglumine), N-ethyl-D-glucamine (i.e. Eglumine), glucosamine, disodium-N-stearoyl-glutamate, heterocyclic amine derivatives such as piperazine or its hexahydrate, N-methylpiperazine, morpholine, 1-(2-hydroxyethyl)pyrrolidine, alkali salts of citric acid, tartaric acid, caproic acid or fatty acids, alkali metal phosphates, silicates or carbonates, sodium, potassium, magnesium, calcium or aluminium hydroxides and organic amines such as ethylamine, dicyclohexylamine or triethanolamine, or alkaline ammonium salts.

The core material as such should be an alkaline reacting core material, i.e. the amount of alkaline reacting compound(s) available in the core material should be enough to form a salt between the enteric coating polymer(s) and the alkaline reacting compound(s).

Thus, the concentration of alkaline reacting compound(s) in the core material (before applying the enteric coating polymer) is from approximately 0.1 mmol/g dry ingredients in the alkali containing part of the core material up to approximately 15 mmol/g, preferably the concentration shall be more than 0.3 mmol/g dry ingredients in the alkaline part of the core material.

The upper limit range is only restricted by the need to include a pharmaceutically active ingredient and excipients such as binders etc in the alkaline core material. The concentration of alkaline reacting compound(s) may be illustrated as follows. For a core material where, for instance, 10 % w/w of a proton pump inhibitor and 5 % w/w of excipients (binders, surfactants etc) are to be included, 85 % w/w remains to possible disposition to the alkaline reacting compound(s). For such a core material, this means that, if the alkaline reacting compound is sodium bicarbonate which has the rather low molecular weight of 84 u, the concentration of the alkaline material in the core material will be $[(85/84)/100] \times 1\,000$, i.e. approximately 9.9 mmol/g in the alkali containing part/layer.

One or more enteric coating layers are applied onto the prepared core material or tablets by using a suitable aqueous coating technique. The enteric coating material is dispersed and/or dissolved in an aqueous vehicle. As enteric coating polymer(s) one or more, separately or in combination, of the following can be used; methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating polymer(s).

The enteric coating layer(s) may contain pharmaceutically acceptable plasticizers to obtain desired mechanical properties, such as flexibility and hardness of the enteric coating layer(s). The amount of plasticizer is optimized for each enteric coating formulation, in relation to selected enteric coating polymer(s), selected plasticizer(s) and the applied amount of said polymer(s). The mechanical properties of the enteric coating are especially important for a tableted multiple unit dosage form, i.e. the individually enteric coated units must withstand

the compression into a tableted multiple unit dosage form without any significant effect on the acid resistance. Suitable plasticizers are for instance, but not restricted to, triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or other plasticizers.

5

The preparation of the core material containing the proton pump inhibitor and alkaline reacting compound(s) is described more in detail below. The individually enteric coated cores can be constituted according to different principles.

- 10 The active substance, the proton pump inhibitor, used as a racemate or one of its single enantiomers or an alkaline salt of said compound or one of its single enantiomers, mixed with the alkaline reacting compound(s) is applied on seeds and are used for further processing.
- 15 The seeds, which are to be layered with the active substances, can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or in mixtures or water soluble seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures. Further, the seeds may comprise active substance in the form of crystals, agglomerates, compacts etc. The size of the seeds is not essential for
- 20 the present invention but may vary between approximately 0.1 and 2 mm. The seeds layered with active substance are produced either by powder or solution/suspension layering using for instance granulating or spray coating/layering equipment.

- Before the seeds are layered, the active substance is mixed with alkaline reacting
- 25 compound(s) and further components to obtain preferred handling and processing properties and suitable concentration of the active substance. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives, can be used. Binders are for example celluloses such as hydroxypropyl methylcellulose, hydroxypropyl cellulose and carboxymethylcellulose
- 30 sodium, polyvinylpyrrolidone, sugars, starches and other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of

pharmaceutically acceptable non-ionic or ionic surfactants such as a for instance sodium lauryl sulfate or polysorbates.

Alternatively, the active substance mixed with alkaline compound(s) and further mixed with
5 suitable constituents can be formulated into tablets or individual cores. Said tablets or cores may be produced by compression/extrusion/spheronization or balling utilizing different processing equipments. The manufactured tablets or cores can further be layered with additional ingredients comprising active substance and alkaline reacting compound(s) and/or be used for further processing.

10 The active substance may optionally be mixed with alkaline pharmaceutically acceptable substance (or substances) for further stabilisation. Such substances can be chosen among, but are not restricted to, substances such as for instance the above mentioned alkaline reacting compounds or other alkaline reacting substances known by the skilled person in the
15 art to be useful as stabilizers for acidic susceptible substances.

Alternatively, the aforementioned alkaline reacting core material can be prepared by the use of spray drying or spray congealing technique.

20 The prepared alkaline reacting core material in the form of tablets or pellets are spray coated with an aqueous enteric coating polymer dispersion/solution. The process parameters such as inlet air temperature, air flow, atomizer air flow and spraying rate are adjusted with respect to the equipment used for the process as well as the specific enteric coating polymer(s). The inlet air temperature must not be such that the enteric coating
25 polymer(s) will block in the spraying nozzles.

The invention is described more in detail by the following examples, which are not intended to limit the scope of the invention.

Example 1

Tablets containing lansoprazole and arginine are produced according to the following procedure. Firstly, dry ingredients are thoroughly mixed and then granulated with a solution
5 in a laboratory mixer. The dried granules are mixed with lubricants etc. in a final mixing step.

<u>Dry ingredients for granulation</u> (for approx. 4000 tablets)		<u>Concentration</u> (mmol/g dry ingredients in the alkaline tablet core)
Lansoprazole	40.4 g	
L-arginine (passing 120 mesh)	365.4 g	4.2
Microcrystalline cellulose	38.5 g	
<u>Granulating solution</u>		
Distilled water	173 g	
Corn starch	7.7 g	

20 The solution is poured over the premixed powder mass during mixing. The wet granules are dried on a tray in a drying cabinet. The dried granules are milled to pass a 1.0 mm sieve. The granules are mixed with

Talc	3.1 g
25 Sodium dodecyl sulphate	20.8 g
Microcrystalline cellulose	19.2 g
Magnesium stearate	5.0 g

in a laboratory mixer, and then compressed into tablets having a size of 7 mm Ø and a
30 weight of approximately 125 mg. The obtained tablets have a content of lansoprazole of 10 mg per tablet.

Obtained tablets are spray coated with the enteric coating dispersion defined below, in a Wurster equipped fluidized bed.

5 Enteric coating dispersion

Water	80.0 g
Triethylcitrate	1.3 g
Na-laurylsulphate	0.2 g
Hydroxypropylmethylcellulose	
10 acetate succinate LF	6.3 g
Talc	1.9 g

This single coating step resulted in tablets having two polymeric layers with different characteristics. The inner layer is not soluble in acetone, as the outer layer, but soluble in
15 water. Figure 1, obtained with confocal laser scanning microscopy (CLSM) shows a cross-section of the tablet where the separating layer is easily detected as a layer having an intense fluorescence.

The separating layer is spontaneously formed in situ during the process, as a salt between
20 the alkaline reacting compound and the enteric coating polymer.

Example 2

Core material containing the magnesium salt of (-)-omeprazole and the alkaline reacting
25 compound trometamine (= tris-buffer) is prepared by extrusion and spheronization.

The powder mass is mixed in a laboratory mixer and then water is added.

Powder mixtureConcentration

(mmol/g dry ingredients in
the alkaline core material)

5	Magnesium salt of (-)-omeprazole	400 g	
	Microcrystalline cellulose	300 g	
	Trometamine	1000 g	4.1
	PVP-XL	100 g	
	Mannitol pwd	195 g	
10	Hydroxypropyl methylcellulose 6 cps	5 g	
	Water	q.s.	

The powder mixture is mixed with the water and the wet mass is mixed to obtain a suitable consistency of the mass.

15

Extrusion is performed with an extruder fitted with 1.0 mm screen. The extrudate is formed into pellets on a spheronizer and dried in a fluidized bed drier.

200 g of the obtained pellets are spray coated with the enteric coating dispersion described below, in a Wurster equipped fluidized bed.

20

Enteric coating dispersion

	Water	93.9 g
	Polyethylene glycol 400	4.6 g
25	Eudragit [™] L30D-55	151.5 g

This single coating step resulted in pellets having two polymeric layers with different characteristics. The inner layer is not soluble in acetone as the outer layer, but soluble in water. The separating layer is spontaneously formed in situ during the process, as a salt between the alkaline reacting compound and the enteric coating polymer.

30

Enteric coated pellets having a separating layer are obtained. These pellets may be filled in capsules or sachets for oral administration.

5 Example 3

Core material containing omeprazole and N-methyl-D-glucamine (=meglumine) is prepared by extrusion and spheronization of the below described composition using the same procedure as in Example 2;

10

Powder mixture

Concentration

(mmol/g dry ingredients in
the alkaline core material)

15	Omeprazole	100.0 g	
	Microcrystalline cellulose	50.0 g	
	Meglumine	500.0 g	2.6
	Mannitol pwd	297.0 g	
	Sodium starch glycolate	48.0 g	
20	Sodium laurylsulphate	5.0 g	
	Water	q.s.	

Obtained dried pellets/cores are spray coated with the enteric coating dispersion described below, in a Wurster equipped fluidized bed.

25

Enteric coating dispersion

	Water	93.9 g
	Polyethylene glycol 400	4.6 g
	Eudragit [™] L30D-55	151.5 g

30

This single coating step resulted in tablets having two polymeric layers with different characteristics. The inner layer is not soluble in acetone, as the outer one, but soluble in water. The separating layer is spontaneously formed in situ during the process, as a salt between the alkaline reacting compound and the enteric coating polymer.

5

The obtained pellets having a separating layer and an enteric coating layer, are suitable for filling into hard gelatine capsules or sachets for oral administration.

Example 4

10

Core material containing magnesium salt of omeprazole and N-methyl-D-glucamine (meglumine) is prepared by layer coating in a Wurster equipped fluidized bed on sugar seeds. For this operation the following materials are used;

15	<u>Substance</u>	<u>Amount</u>	<u>Concentration</u> (mmol/g dry ingredients in the alkali containing layer)
	Water purified	102 g	
	Ethanol 99% (w/v)	102 g	
20	HPMC 6 cps	2 g	
	N-methyl-D-glucamine	3.3 g	0.37
	Magnesium salt of omeprazole	40 g	
	Non Pareille	500 g	

25 First the water and ethanol were mixed whereafter the HPMC was dissolved in the obtained solution. N-methyl-D-glucamine and magnesium salt of omeprazole were dissolved/suspended in the solution. The sugar cores (Non Pareille) were used as starting seeds for the formation of core material. A peristaltic pump was used to feed the spraying suspension, which was fed with a velocity of 3.9 g/min.

30

The Wurster apparatus was equipped with a 60 mm high insertion tube, having a diameter of 50 mm, positioned to leave a 10 mm slit below it. A spraying nozzle having a 0.8 mm opening was used. The atomizing air flow was 2.3 Nm³/h and air pressure used was 1.9 bar. The inlet air temperature was 50° C and flow used 43 m³/h.

5

After the core formation step, 100 grams of the obtained core material was film-coated by spraying with an enteric coating dispersion as described below, using the same equipment as in the core formation step.

10 Enteric coating dispersion

Water purified	183 g
Triethyl citrate	2.9 g
Sodium laurylsulphate	0.4 g
15 Hydroxypropyl methylcellulose	
acetate succinate LF	14.4 g
Talc	4.3 g

First the triethyl citrate was dissolved in the water, and thereafter the sodium laurylsulphate was added. The hydroxypropylmethylcellulose acetate succinate was dispersed in the solution, and then the talc was added. The dispersion was fed with a rate of 3.8 g/min.

20

Inlet air temperature used was 42 ° C and flow was set to 40 Nm³/h. Atomizing air flow used was 2.1 Nm³/h , obtained with a pressure of 1.7 bar.

25

After finalizing the spraying, the inlet air temperature is rised to 60° C and the product is kept at this temperature for appr. 5 minutes.

This single film-coating step resulted in cores having two polymeric coating layers with different characteristics. The inner layer is not soluble in acetone, as the outer layer, but

30

soluble in water. Using confocal laser scanning microscopy to study a cross-section of the cores from this example, the presence of an inner layer was confirmed.

The separating layer is spontaneously formed in situ during the process, as a salt between
5 the alkaline reacting compound and the enteric coating polymer.

Example 5

A roto granulator was used to produce spherical core units containing pantoprazole. As
10 starting material inert sugar seeds (Non-Pareille) with an average size between 0.6 to 0.71 mm Ø was used. The sugar seeds were coating layered with the powder mixture described below, by spraying a 5 % solution of HPMC 6 cps in water.

The obtained core material containing pantoprazole was dried at 40°C for 16 hours in
15 vacuum and then sieved to give granules between 0.6 mm to 1.25 mm Ø .

Starting material

Non-Pareille 110 parts by weight

20	<u>Powder mixture</u>	<u>Amount</u>	<u>Concentration</u>
			(mmol/g dry ingredients in the alkali containing layer)
	Pantoprazole	29.3 parts by weight	
25	L-Lysine	22.0 "	0.88
	Sucrose	36.7 "	
	Corn starch	42.5 "	
	Microcrystalline cellulose	36.7 "	

Solution

Hydroxypropyl methylcellulose 2.9 “
Water (58.7 “)

- 5 250 g of the core material produced in this way was spray coated with an enteric coating dispersion in a Wurster equipped fluidized bed apparatus. The dispersion was made by adding the mentioned ingredients in stated order, while stirring.

Dispersion

10	Water	626.8 g
	Triethylcitrate	9.8 g
	Sodium-laurylsulphate	1.5 g
	Hydroxypropylmethylcellulose	
	acetate succinate LF	49.2 g
15	Talc	14.8 g

Enteric coated pellets having a water soluble separating layer were obtained. These pellets may be filled in capsules or sachets for oral administration.

20 Example 6

Omeprazole tablets, 6 mm in diameter containing 20 mg of omeprazole were prepared by mixing and granulating dry powder ingredients with water in a Kenwood mixer. For this operation the following materials are used;

	<u>Substance</u>	<u>Amount</u>	<u>Concentration</u> (mmol/g dry ingredients in the alkaline tablet core)
	Omeprazole	40.0 g	
5	Mannitol pwd	68.0 g	
	Microcrystalline cellulose	35.0 g	
	Polyvinylpyrrolidone cross-linked	30.0 g	
	Hydroxypropylcellulose low-substituted	20.0 g	
	L-arginine	5.3 g	0.14
10	Sodium laurylsulphate	2.0 g	
	Water purified q.s.	approx 50 g	
	Sodium stearyl fumarate (SSF)	1.0 g	

The dry powders except for SSF were mixed to homogeneity. This mixture was moistened
15 with the water and the wet mass dried on a tray in a drying oven. The obtained granules
were milled to pass a screen with 0.8 mm apertures. Then the lubricant SSF was mixed with
the granules using the same Kenwood mixer as before.

Cores having an average weight of 101 mg were compressed on a tableting machine
20 equipped with 6mm diameter punches.

After the core formation step, 50 grams of the obtained cores were film-coated by spraying
an aqueous enteric coating dispersion as described below, using a Wurster equipped
fluidized bed.

Enteric coating dispersion

<u>Substance</u>	<u>Amount</u>
Water purified	183 g
Triethyl citrate	2.9 g
5 Sodium laurylsulphate	0.4 g
Hydroxypropylmethylcellulose acetate succinate LF	14.4 g
Talc	4.3 g

10

This single film-coating step resulted in cores having two polymeric coating layers with different characteristics. The inner layer is not soluble in acetone, as the outer layer, but soluble in water.

15 The separating layer is spontaneously formed in situ during the process, as a salt between the alkaline reacting compound and the enteric coating polymer.

Example 7

20 Tablets, 7 mm in diameter containing omeprazole and disodiumhydrogenphosphate was prepared by mixing and granulating dry powder ingredients with a water solution containing sodium laurylsulphate, in a Kenwood mixer. For this operation the following materials are used:

25

24

<u>Substance</u>	<u>Amount</u>	<u>Concentration</u> (mmol/g dry ingredients in the alkaline tablet core)
Omeprazole	80 g	
5 Mannitol pwd	88 g	
Microcrystalline cellulose	132 g	
L-HPC	53 g	
Disodiumhydrogenphosphate dihydrate	104 g	1.12
10 <u>Granulation liquid</u>		
Water purified	80 g	
Sodium laurylsulphate	3 g	
Water purified q.s.		
15 <u>Final mixing</u>		
Sodium stearyl fumarate (SSF)	10 g	
Polyvinylpyrrolidone crosslinked	50 g	

20 The dry powders except for SSF were mixed to homogeneity. This mixture was moistened first with the granulation liquid and then with water until satisfactory consistency of the mass. The wet mass was dried on a tray in a drying oven. The obtained granules were milled to pass a screen with 0.8 mm apertures and then the lubricant SSF and the disintegrating agent polyvinylpyrrolidone crosslinked were mixed with the obtained granules using the

25 same Kenwood mixer as before.

Cores having an average weight of 130 mg were compressed on a tableting machine equipped with 7 mm diameter punches.

After the core formation step, 50 grams of the obtained cores were film-coated by spraying with an aqueous enteric coating dispersion as described below, using a Wurster equipped fluidized bed.

5 Enteric coating dispersion

	Water purified	183 g
	Triethyl citrate	2.9 g
	Sodium laurylsulphate	0.4 g
10	Hydroxypropyl methylcellulose	
	acetate succinate LF	14.4 g
	Talc	4.3 g

15 This single film-coating step resulted in cores having two polymeric coating layers with different characteristics. The inner layer is not soluble in acetone, as the outer layer, but soluble in water. The separating layer is spontaneously formed in situ during the process, as a salt between the inorganic alkaline reacting compound and the enteric coating polymer.

Reference Examples 1 and 2

20

Placebo tablets, 6 mm in diameter was prepared by mixing and granulating dry powder ingredients with water in a Kenwood mixer. For this operation the following materials are used;

	<u>Substance</u>	<u>Amount</u>	<u>Concentration</u> (mmol/g dry ingredients in the alkali containing layer)	
			Ref.Ex. 1	Ref.Ex.2
5	Mannitol pwd	161.5 g	141.3 g	
	Microcrystalline cellulose	38.5 g	38.5 g	
	Na ₂ HPO ₄ ·2H ₂ O	-----	20.2 g	----- 0.56
	Water purified q.s. approx	45 g	45 g	
	Sodium stearyl fumarate (SSF)	1.0 g	1.0 g	

10

The dry powders except for SSF were mixed to homogeneity. This mixture was moistened with the water and the wet mass dried on a tray in a drying oven. The obtained granules were milled to pass a screen with 0.8 mm apertures. Then the lubricant SSF was mixed with the granules using the same Kenwood mixer as before.

15

Cores having an average weight of 93- 94 mg were compressed on a tableting machine equipped with 6 mm diameter punches.

After the core formation step, 50 grams of each kind of the obtained cores were (separately) film-coated by spraying an aqueous enteric coating dispersion according to below, using a Wurster equipped fluidized bed.

<u>Enteric coating dispersion</u>	
<u>Substance</u>	<u>Amount</u>
25 Water purified	183 g
Triethyl citrate	2.9 g
Sodium laurylsulphate	0.4 g
Hydroxypropylmethylcellulose acetate succinate LF	14.4 g
30 Talc	4.3 g

These reference examples show that presence of the alkaline material in the core material composition is necessary for the formation of an in situ formed spontaneously developed separating layer.

5

For Reference Ex. 1, this single film-coating step resulted in cores having only one coating layer, being soluble in acetone. No separating layer was spontaneously formed.

10

For Reference Ex. 2, this single film-coating step resulted in cores having two polymeric coating layers with different characteristics. The inner layer is not soluble in acetone, as the outer layer, but soluble in water. The separating layer is spontaneously formed in situ during the process, as a salt between the alkaline reacting compound and the enteric coating polymer.

15

By using confocal laser scanning microscopy to study a cross-section of the cores from the Reference example 2, the presence of an inner layer was confirmed. In contrast, examining a cross-section of a core from Reference example 1, no inner layer was seen.

20

The best mode to practice the invention is by the formulations described in Examples 1 and 2.

The different active substances, i.e. proton pump inhibitors, are prepared according to information disclosed in the Patent specifications mentioned in page 6 of this specification.

Claims

1. An oral pharmaceutical dosage form comprising a core material that contains a proton pump inhibitor, one or more alkaline reacting compound(s) and optionally pharmaceutically acceptable excipients having a water soluble separating layer and an enteric coating layer
5 characterized in that the core material is alkaline reacting and that the separating layer is being formed in situ during the enteric coating as a water soluble salt between the enteric coating layer polymer(s) and the alkaline reacting compound(s).
- 10 2. A dosage form according to claim 1, wherein the alkaline reacting compounds are selected from the group of alkaline organic substances, hydroxides of alkali metals or one of their alkaline salts of phosphoric acid, carbonic acid or silicic acid, or an alkaline ammonium salt.
- 15 3. A dosage form according to claim 2, wherein the alkaline reacting substance is a hydroxide of an alkali metal or an alkaline salt of phosphoric acid, carbonic acid or silicic acid, or an alkaline ammonium salt.
4. A dosage form according to claim 2, wherein the alkaline reacting compound is an
20 alkaline organic substance, e.g. an amino acid or a salt thereof, an alkaline amine or a derivative thereof, or an alkaline salt of a weak organic acid.
5. A dosage form according to claim 2, wherein the alkaline organic substance is an amino acid, e.g. lysine, arginine, ornithine or histidine, or an alkaline amine or a derivative
25 thereof, e.g. N-methyl-D-glucamine or trometamine.
6. A dosage form according to claim 1, wherein the alkaline reacting compounds are present in a concentration of more than 0.1 mmol/g dry ingredients in the alkaline part of the core material.

7. A dosage form according to claim 1, wherein the enteric coating polymer(s) is/are hydroxypropyl cellulose derivative(s), e.g. hydroxypropylmethylcellulose acetate succinate.

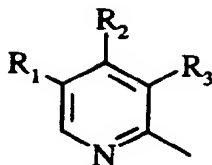
8. A dosage form according to claim 1, wherein the enteric coating polymer is copolymerized methacrylic acid/methacrylic acid methyl esters.

9. A dosage form according to claim 1, wherein the proton pump inhibitor is a compound of the general formula I or a pharmaceutically acceptable salt thereof or a pure enantiomer thereof in neutral form or in the form of an alkaline salt

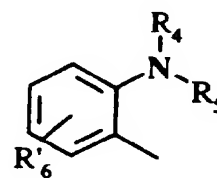


wherein

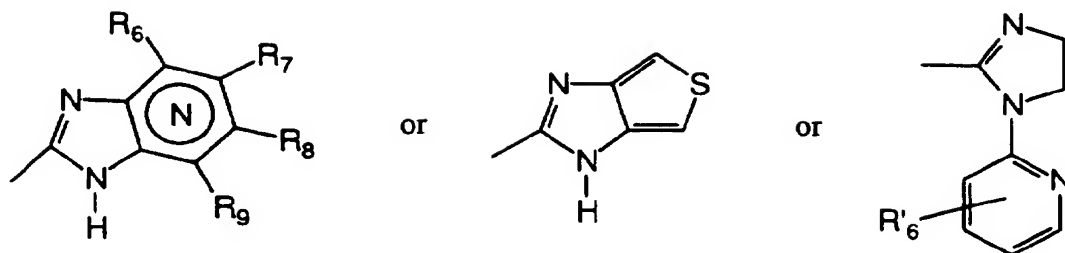
Het₁ is



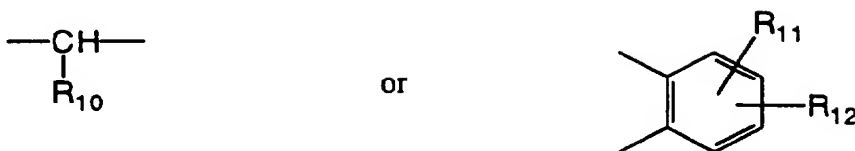
or



Het₂ is



X =



5 wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R₆-R₉ optionally may be exchanged for a nitrogen atom without any substituents;

10 R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R₄ and R₅ are the same or different and selected from hydrogen, alkyl and aralkyl;

15

R'₆ is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R₆-R₉ are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R₆-R₉ form ring structures which may be further substituted;

20

R₁₀ is hydrogen or forms an alkylene chain together with R₃ and

R₁₁ and R₁₂ are the same or different and selected from hydrogen, halogen or alkyl and alkyl groups, alkoxy groups and moities thereof may be branched and straight C₁-C₉ -chains or comprise cyclic alkyl groups, for example cycloalkylalkyl.

5

10. A dosage form according to claim 1, wherein the proton pump inhibitor is omeprazole or an alkaline salt thereof.

10

11. A dosage form according to claim 1, wherein the proton pump inhibitor is a pure enantiomer of omeprazole or an alkaline salt thereof.

12. A dosage form according to claim 1, wherein the proton pump inhibitor is lansoprazole, one of its pure enantiomers or a pharmaceutically acceptable salt thereof.

15

13. A dosage form according to claim 1, wherein the proton pump inhibitor is pantoprazole, one of its pure enantiomers or a pharmaceutically acceptable salt thereof.

20

14. A dosage form according to claim 1, wherein the alkaline reacting core material is individual pellets intended for a capsule formulation or a tableted multiple unit dosage form.

15. A dosage form according to claim 1, wherein the alkaline reacting core material is a tablet.

25

16. A dosage form according to claim 1, wherein individually enteric coated pellets are compressed into a tableted multiple unit dosage form.

30

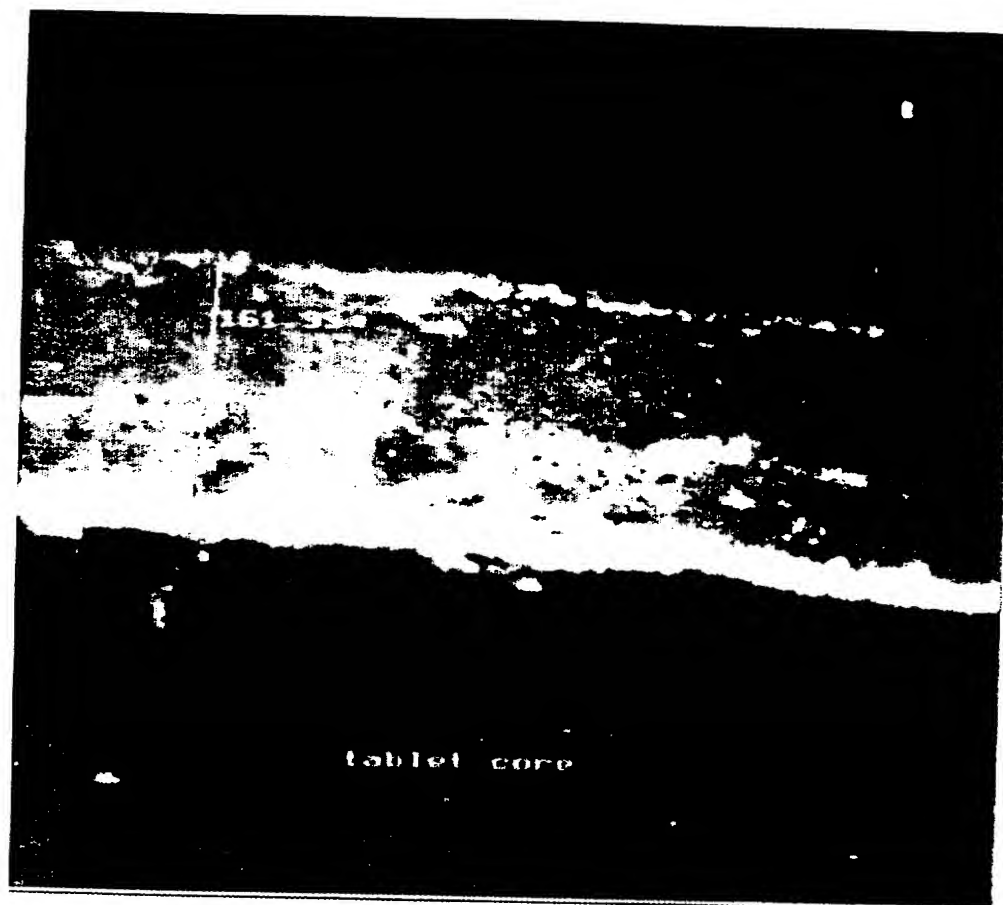
17. A process for the preparation of an oral, enteric coated pharmaceutical dosage form comprising a core material that contains a proton pump inhibitor, one or more alkaline reacting compounds and optionally pharmaceutically acceptable excipients having a water

soluble separating layer and an enteric coating layer characterized in that an alkaline reacting core material is prepared and coated with an enteric coating polymer wherein a separating layer between the core material and the enteric coating layer is formed in situ by a reaction between the enteric coating polymer(s) and the alkaline reacting compound(s) in the core material during the application of the enteric coating onto the alkaline reacting core material.

18. An oral, pharmaceutical dosage form comprising a proton pump inhibitor as defined in any of claims 1-16 for use in inhibiting gastric acid secretion in mammals and man.
19. A method for inhibiting gastric acid secretion in mammals and man by administering to a host in need thereof a dosage form comprising a therapeutically effective dose of a proton pump inhibitor as defined in any of claims 1-16.
20. Use of an oral pharmaceutical dosage form defined in any of claims 1 - 16 for the manufacture of a medicament useful in the treatment of gastric acid related diseases.

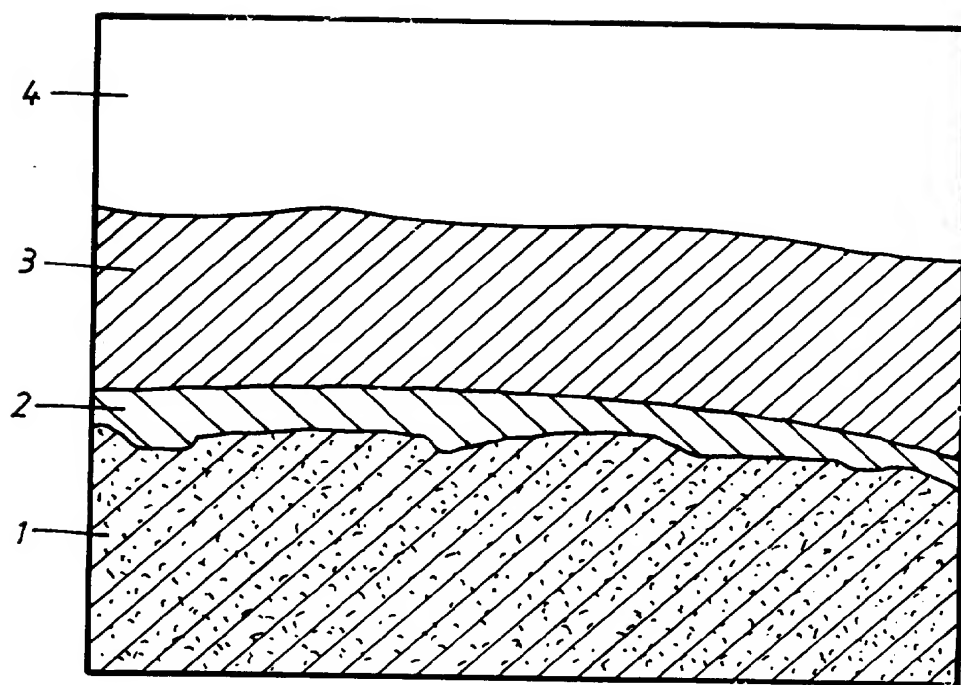
1 / 2

Fig. 1



2 / 2

Fig. 2



INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/00161

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/30, A61K 31/44, A61K 47/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, WPIL, USFULLTEXT, CAPLUS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0247983 A2 (AKTIEBOLAGET HÄSSLE), 2 December 1987 (02.12.87) --	1-18,20
A	Dialog Information Services, File 351, Word Patent Index 81-95, Dialog accession no. 009584650, WPI accession no. 93-278196/35, Yoshitomi Pharm Ind KK: "Anti-ulcer agent- contains benzimidazole cpd., amino acid and buffer, giving good stability", JP 5194225, A, 930803, 9335 (Basic) --	1-18,20
A	EP 0365947 A1 (PHARMACIA AB), 2 May 1990 (02.05.90) -- -----	1-18,20

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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10 -05- 1996

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INTERNATIONAL SEARCH REPORT

Inte: onal application No.

PCT/SE 96/00161

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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See PCT Rule 39.1(iv): Method for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

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2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

01/04/96

PCT/SE 96/00161

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A2- 0247983	02/12/87	SE-T3- 0247983	
		AR-A- 240250	30/03/90
		AU-B,B- 601974	27/09/90
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		CA-A- 1292693	03/12/91
		DE-A- 3783394	18/02/93
		DK-B- 169988	24/04/95
		EP-A,A,A 0496437	29/07/92
		EP-A,A- 0567201	27/10/93
		ES-T- 2006457	01/01/94
		GB-A- 2189698	04/11/87
		HK-A- 135294	09/12/94
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		SG-A- 154294	17/03/95
		SU-A- 1820837	07/06/93
		US-A- 4786505	22/11/88
EP-A1- 0365947	02/05/90	SE-T3- 0365947	
		AU-B,B- 612525	11/07/91
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		SE-A- 8803822	26/10/88
		SG-A- 123894	17/03/95
		US-A- 5178868	12/01/93

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 45/06, 31/44, 31/71, 31/41, 31/43, 9/20, 9/48		A1	(11) International Publication Number: WO 96/24375
			(43) International Publication Date: 15 August 1996 (15.08.96)
(21) International Application Number: PCT/SE96/00125			(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KG, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 2 February 1996 (02.02.96)			
(30) Priority Data: 9500422-2 6 February 1995 (06.02.95) SE			
(60) Parent Application or Grant (63) Related by Continuation US 08/464,775 (CIP) Filed on 7 June 1995 (07.06.95)			
(71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).			
(72) Inventors; and (75) Inventors/Applicants (for US only): DEPU, Helene [FR/SE]; Wrangelsgatan 7B, S-416 62 Göteborg (SE). ROSINSKI, Adam [SE/SE]; Råvekärsgatan 307, S-431 33 Mölndal (SE).			
(74) Agent: PATENT DEPARTMENT; Astra Aktiebolag, S-151 85 Södertälje (SE).			
(54) Title: NEW ORAL PHARMACEUTICAL DOSAGE FORM			
(57) Abstract An oral pharmaceutical dosage form comprising an acid susceptible proton pump inhibitor and one or more antibacterial compounds in a fixed formulation. The fixed formulation is intended for oral use and in the form of an enteric coating layered tablet, a capsule or a multiple unit tableted dosage form. The multiple unit dosage form is most preferred. The new fixed formulation is especially useful in the treatment of disorders associated with <i>Helicobacter</i> infections.			

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NEW ORAL PHARMACEUTICAL DOSAGE FORM

Field of the invention

5 The present invention is related to new oral pharmaceutical preparations especially for use in the treatment of disorders associated with *Helicobacter* infections. The present preparations comprise an acid susceptible proton pump inhibitor in combination with one or more antibacterial compounds in a new fixed unit dosage form, especially a tableted dosage form. Furthermore, the present invention refers to a method for the manufacture of
10 such preparations and the use of such preparations in medicine, especially in the treatment of *Helicobacter pylori* infections.

Background of the invention

15 The relationship between gastrointestinal disorders and infections with *Helicobacter pylori* proposed in 1983 by Warren (Warren JR Lancet 1983;1.1273) is well established today. A number of different therapies have been proposed for treatment of *H. pylori* infections. Most of these therapies comprise different combinations of antibacterial compounds. Some of these therapies also comprise a bismuth compound, see for instance WO 89/03219
20 (Borody). Other combination therapies comprise a proton pump inhibitor and one or more antibacterial compounds, for instance a combined regimen of omeprazole and amoxicillin which has been approved by regulatory authorities in for example Great Britain and Sweden for the treatment of *H. pylori* infections. Different triple therapies, for example omeprazole, clarithromycin and amoxicillin or other antibacterial substances, have recently
25 been reported at the 10th World Congresses of Gastroenterology in October 1994. Some published patent applications in this field are for instance:

WO 93/00327, Astra Aktiebolag, which discloses the combination of a substance with inhibiting effect on the gastric acid secretion which increases the intragastric pH and an

acid degradable antibacterial compound. The proposed combination is especially suitable for the treatment of *H. pylori* infections.

WO 92/03135, Smithkline & French Laboratories, which discloses a combination of a
5 benzimidazole and an anti-*Helicobacter* agent, i.e. for instance pantoprazole in combination with amoxicillin and/or metronidazole.

In these proposed combination therapies each single active substance is administered separately in different dosage forms, each one comprising only one single active substance.
10 It is well known that patient compliance is a main factor in receiving a good result in medical treatments, especially in the treatment of *H. pylori* infections. Administration of two, three or even more different tablets to the patient is not convenient or satisfactory to achieve the most optimal results. The present invention now provides new oral dosage forms comprising two or more different active substances combined in one fixed unit
15 dosage form, preferably a tablet.

It is well known that proton pump inhibitors are susceptible to degradation/transformation in acid reacting and neutral media. In respect of the stability properties, it is obvious that one of the active substances being a proton pump inhibitor must be protected from contact
20 with acidic gastric juice by an enteric coating layer. There are different enteric coating layered preparations of omeprazole as well as other proton pump inhibitors described in the prior art, see for example US-A 4,786,505 (AB Hässle).

There are problems to produce a fixed unit dosage form comprising a rather high amount of
25 active substances. Different active substances in the same preparation give further problems. Preparation of a multiple unit tableted dosage form arises specific problems when enteric coating layered pellets containing acid susceptible proton pump inhibitors as active substance are compressed into tablets. If the enteric coating layer does not withstand the compression of the pellets into a tablet the susceptible active substance will be

destroyed upon administration by penetrating acidic gastric juice, i.e. the acid resistance of the enteric coating layer of the pellets will not be sufficient in the tablet after compression.

Summary of the invention

5

The present invention provides oral, fixed unit dosage forms, i.e. multiple unit tableted dosage forms, enteric coating layered tablets, multilayered tablets or a capsule filled with more than one pharmaceutically active compound. The active compounds present are preferably an acid susceptible proton pump inhibitor and one or more antibacterial substances. These new dosage forms will simplify the regimen and improve the patient compliance.

10

Description of the Figures

15

Fig. 1 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor in the form of enteric coating layered pellets (1) in admixture with an antibacterial granulation (2). The tablet is covered by an overcoating layer (7).

20

Fig. 2 illustrates a cross-section of a tablet with two separate layers, one layer comprises enteric coating layered pellets of an acid susceptible proton pump inhibitor (1) in admixture with excipients (3) and the other layer comprises the antibacterial compound(s) (2). The tablet is covered by an overcoating layer (7).

25

Fig. 3 illustrates a cross-section of an enteric coating layered tablet comprising an acid susceptible proton pump inhibitor in admixture with one or more antibacterial substances (4). The tablet is covered by an enteric coating layer (7).

Fig. 4 illustrates an enteric coating layered tablet consisting of two separate layers, one layer comprises an acid susceptible proton pump inhibitor (5) and the other layer comprises the antibacterial compound(s) (6).

5 Detailed description of the invention

One object of the invention is to provide an oral, multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor in the form of individually enteric coating layered units together with one or more antibacterial compounds in the form of a powder or granules compressed into a tablet. The enteric coating layer(s) covering the individual units of the acid susceptible proton pump inhibitor has properties such that the compression of the units into a tablet does not significantly affect the acid resistance of the individually enteric coating layered units. Furthermore, the multiple unit tableted dosage form provides a good stability during long-term storage to the active substances.

15 Alternatively, the prepared tablet has separate layers, one layer is in the form of compressed enteric coated layered units comprising the proton pump inhibitor and another layer comprises the antibacterial compound(s).

The new fixed dosage form is preferably in the form of a multiple unit tableted dosage form comprising enteric coating layered units of the one of the active substance which is acid susceptible, i.e. the proton pump inhibitor, and granules of the other active substance(s), i.e. the antibacterial granulation, as shown in Figs. 1 and 2. Alternatively, the different active compounds may be intimately mixed with each other and compressed into a conventional tablet, which is enteric coated as shown in Figs. 3 and 4. As a further alternative, the different active substances are dry mixed and filled into a capsule. In the latter preparation the acid susceptible proton pump inhibitor is in the form of enteric coating layered units (1).

20

25

Another object of the invention is to provide a tablet preparation comprising an acid susceptible proton pump inhibitor in admixture with one or more antibacterial substances compressed into a tablet, which tablet is enteric coating layered. Optionally a separating layer is applied before the tablet is enteric coating layered. Alternatively, the prepared
5 tablet core has separate layers, each one comprising different active substances. One of the layers comprises the acid susceptible proton pump inhibitor and another layer(s) comprises(-e) the antibacterial substance or substances, respectively. The prepared tablet is thereafter enteric coating layered.

10 A further object of the invention is to provide a dosage form which is divisible, such as divisible tablets.

Still a further object of the invention is to provide a multiple unit tableted dosage form, which is divisible and easy to handle. The multiple unit tableted dosage form may be
15 dispersed in an aqueous liquid and can be given to patients with swallowing disorders and in pediatrics. Such a suspension of dispersed units/pellets of appropriate size can be used for oral administration and also for feeding through a naso-gastric tube.

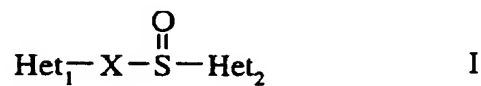
Furthermore, the present invention provides a capsule preparation comprising the acid
20 susceptible proton pump inhibitor in the form of enteric coating layered pellets mixed with one or more antibacterial compounds in the form of granules or pellets.

The antibacterial components may be formulated in the form of instant release, sustained release or extended release formulations. Alternatively, the components may be formulated
25 in an effervescent formulation.

The new fixed unit dosage forms comprise as active substances an acid susceptible proton pump inhibitor and one or more antibacterial compounds. The different active components used in the dosage forms are defined below.

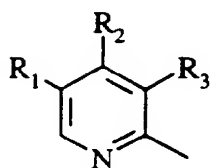
Active substances

The proton pump inhibitors are for example compounds of the general formula I

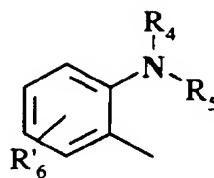


wherein

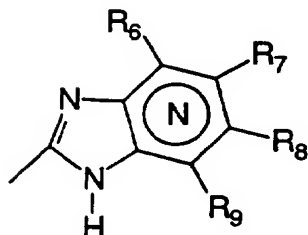
Het₁ is



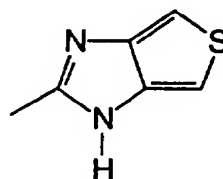
or



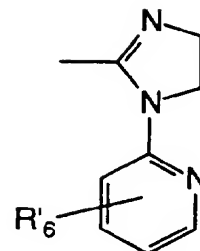
Het₂ is



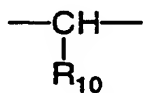
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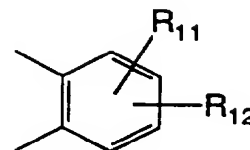
or



X =



or



wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R₆-R₉ optionally may be exchanged for a nitrogen atom without any substituents;

R_1 , R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

5 R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

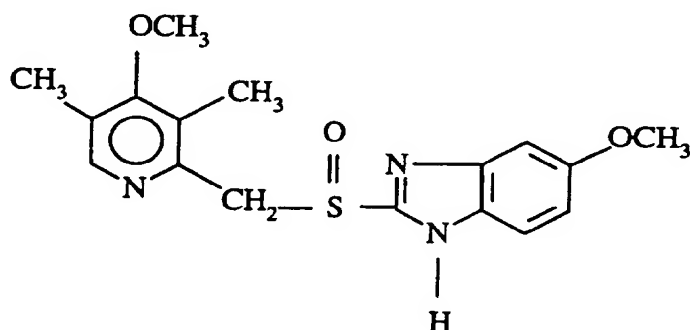
10 R_6 - R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxy carbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6 - R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3 and

15 R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl and alkyl groups, alkoxy groups and moieties thereof may be branched and straight C_1 - C_9 -chains or comprise cyclic alkyl groups, for example cycloalkylalkyl.

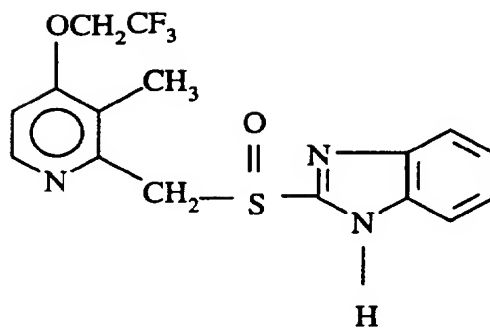
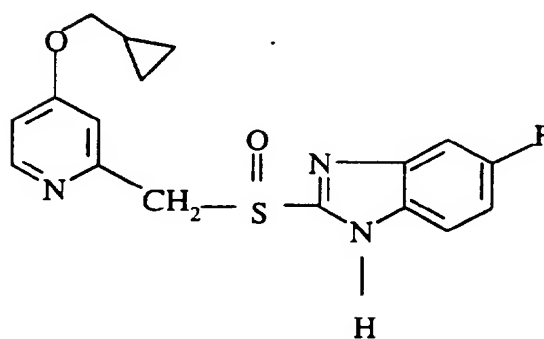
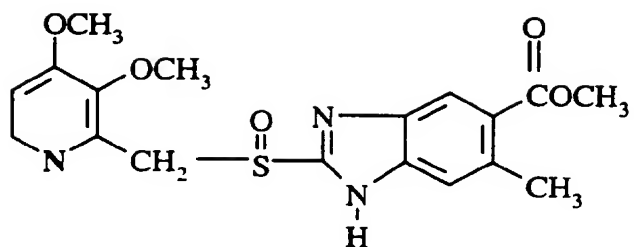
Examples of proton pump inhibitors according to formula I are

20



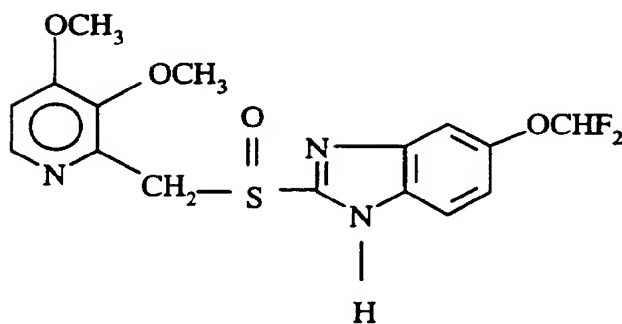
Omeprazole

8

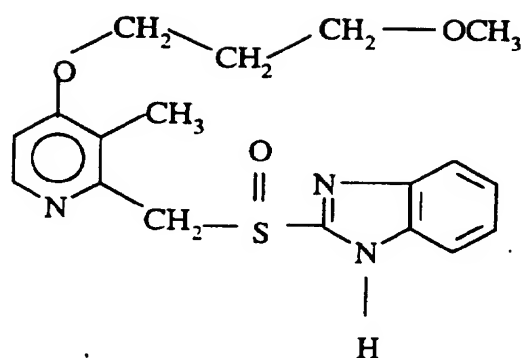


Lansoprazole

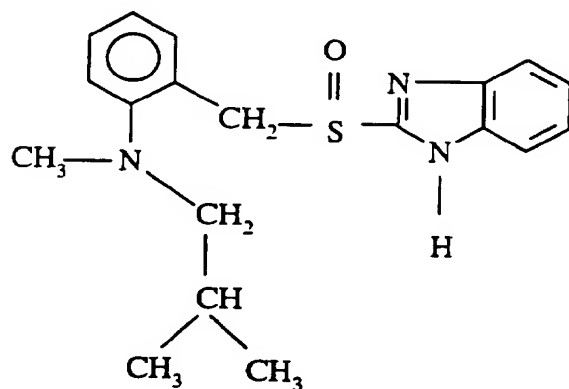
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Pantoprazole

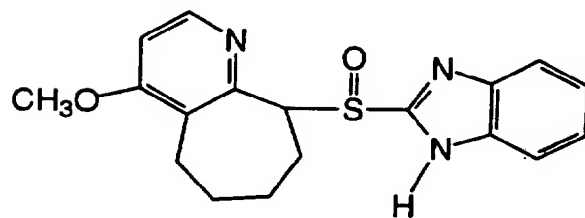
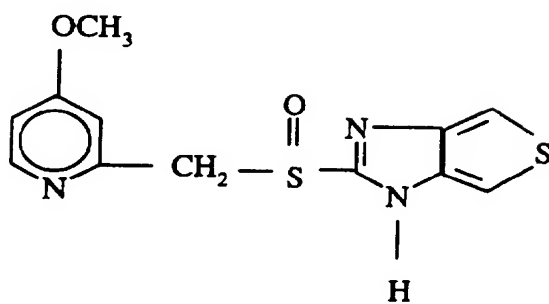


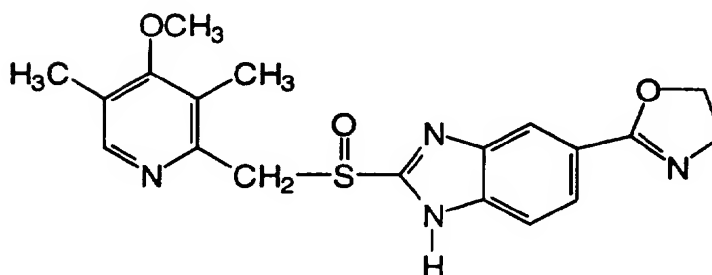
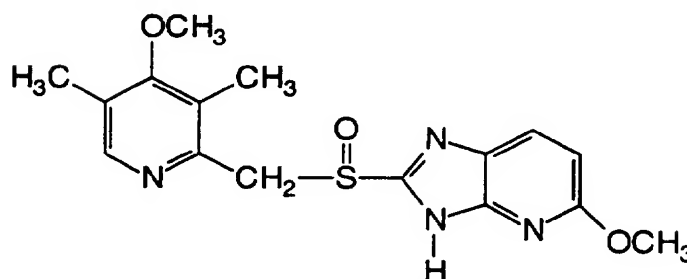
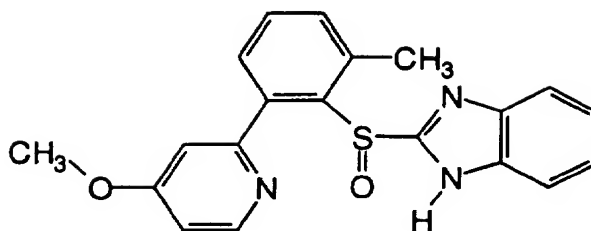
Pariprazole



Leminoprazole

5





5

The proton pump inhibitors used in the dosage forms of the invention may be used in neutral form or in the form of an alkaline salt, such as for instance the Mg^{2+} , Ca^{2+} , Na^+ , K^+ or Li^+ salts, preferably the Mg^{2+} salts. Further where applicable, the compounds listed above
 10 may be used in racemic form or in the form of a substantially pure enantiomer thereof, or alkaline salts of the single enantiomers.

Suitable proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO90/06925, WO91/19711,
 15 WO91/19712, and further especially suitable compounds are described in WO95/01977 and WO94/27988.

A wide variety of antibacterial compounds may be used in combination with a suitable proton pump inhibitor in the fixed unit dosage form according to the present invention. Such antibacterial compounds include for example nitroimidazole antibiotics, tetracyclines, penicillins, cephalosporins, carbopenems, aminoglycosides, macrolide antibiotics,

5 lincosamide antibiotics, 4-quinolones, rifamycins and nitrofurantoin. In the following examples of such antibacterial compounds are listed: ampicillin, amoxicillin, benzylpenicillin, phenoxymethylpenicillin, bacampicillin, pivampicillin, carbenicillin, cloxacillin, cyclacillin, dicloxacillin, methicillin, oxacillin, piperacillin, ticarcillin, flucloxacillin, cefuroxime, cefetamet, cefetrame, cefixime, cefoxitin, ceftazidime, 10 ceftizoxime, latamoxef, cefoperazone, ceftriaxone, cefsulodin, cefotaxime, cephalixin, cefaclor, cefadroxil, cefalothin, cefazolin, cefpodoxime, ceftibuten, aztreonam, tigemonam, erythromycin, dirithromycin, roxithromycin, azithromycin, clarithromycin, clindamycin, paldimycin, lincomycin, vancomycin, spectinomycin, tobramycin, paromomycin, metronidazole, tinidazole, ornidazole, amifloxacin, cinoxacin, 15 ciprofloxacin, difloxacin, enoxacin, fleroxacin, norfloxacin, ofloxacin, temafloxacin, doxycycline, minocycline, tetracycline, chlortetracycline, oxytetracycline, methacycline, rolitetracyclin, nitrofurantoin, nalidixic acid, gentamicin, rifampicin, amikacin, netilmicin, imipenem, cilastatin, chloramphenicol, furazolidone, nifuroxazide, sulfadiazin, sulfametoxazol, bismuth subsalicylate, colloidal bismuth subcitrate, gramicidin, 20 mecillinam, cloxiquine, chlorhexidine, dichlorobenzylalcohol, methyl-2-pentylphenol. The active antibacterial agents could be in standard forms or used as salts, hydrates, esters etc. A combination of two or more of the above listed drugs may be used, for example to minimize the risk for developing resistance. Preferable antibacterial compounds for the new fixed dosage form are clarithromycin, erythromycin, roxithromycin, azithromycin, 25 amoxicillin, metronidazole, tinidazole and tetracycline. Clarithromycin and metronidazole alone or in combination are especially suitable.

The preferred multiple unit tableted dosage form comprising a proton pump inhibitor in the form of a racemat, an alkaline salt or one of its single enantiomers and one or more 30 antibacterial compounds, is characterized in the following way. Individually enteric coating

layered units (small beads, granules or pellets) containing the acid susceptible proton pump inhibitor and optionally containing alkaline reacting substances, are mixed with the antibacterial compound(s) and conventional tablet excipients. Preferably, the antibacterial compound(s) and tablet excipients are in the form of a granulation. The dry mixture of
5 enteric coating layered units, antibacterial granulation and optionally excipients are compressed into the multiple unit tableted dosage forms. With the expression "individual units" is meant small beads, granules or pellets, in the following referred to as pellets of the proton pump inhibitor.

10 The compaction process (compression) for formulating the multiple unit tableted dosage form must not significantly affect the acid resistance of the enteric coating layered pellets. In other words the mechanical properties, such as the flexibility and hardness as well as the thickness of the enteric coating layer(s), must secure that the requirements on enteric coated articles in the United States Pharmacopeia are accomplished in that the acid
15 resistance does not decrease more than 10% during the compression of the pellets into tablets.

The acid resistance is defined as the amount of proton pump inhibitor in the tablets or pellets after being exposed to simulated gastric fluid USP, or to 0,1 M HCl (aq) relative to
20 that of unexposed tablets and pellets, respectively. The test is accomplished in the following way. Individual tablets or pellets are exposed to simulated gastric fluid of a temperature of 37°C. The tablets disintegrate rapidly and release the enteric coating layered pellets to the medium. After two hours the enteric coating layered pellets are removed and analyzed for content of the proton pump inhibitor using High Performance Liquid
25 Chromatography (HPLC).

Further specific components used in the fixed unit dosage forms of the present invention are defined below.

Core material - for enteric coating layered pellets comprising a proton pump inhibitor

The core material for the individually enteric coating layered pellets can be constituted according to different principles. Seeds layered with the acid susceptible proton pump inhibitor, optionally mixed with alkaline substances, can be used as the core material for the further processing.

The seeds which are to be layered with the acid susceptible proton pump inhibitor can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or in mixtures or water-soluble seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures. Further, the seeds may comprise the proton pump inhibitor in the form of crystals, agglomerates, compacts etc. The size of the seeds is not essential for the present invention but may vary between approximately 0.1 and 2 mm. The seeds layered with the proton pump inhibitor are produced either by powder or solution/suspension layering using for instance granulation or spray coating layering equipment.

Before the seeds are layered, the proton pump inhibitor may be mixed with further components. Such components can be binders, surfactants, fillers, disintegrating agents, alkaline additives or other and/or pharmaceutically acceptable ingredients alone or in mixtures. The binders are for example are celluloses such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl-cellulose (HPC), carboxymethylcellulose sodium, polyvinyl pyrrolidone (PVP), sugar or starch or other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic or ionic surfactants such as for instance sodium lauryl sulfate.

Alternatively, the proton pump inhibitor optionally mixed with alkaline substances and further mixed with suitable constituents can be formulated into core material. Said core material may be produced by extrusion/spheronization, balling or compression utilizing

conventional process equipment. The size of the formulated core material is approximately between 0.1 and 4 mm and preferably between 0.1 and 2 mm. The manufactured core material can further be layered with additional ingredients comprising the proton pump inhibitor and/or be used for further processing.

5

The proton pump inhibitor is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and a suitable concentration of the substance in the final mixture. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives.

10

Further, the proton pump inhibitor may also be mixed with an alkaline, pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

15

20

Alternatively, the aforementioned core material can be prepared by using spray drying or spray congealing technique.

25

Enteric coating layer(s)

Before applying the enteric coating layer(s) onto the core material in the form of individual pellets, the pellets may optionally be covered with one or more separating layer(s) comprising pharmaceutical excipients optionally including alkaline compounds such as

30

pH-buffering compounds. This/these separating layer(s), separate(s) the core material from the outer layers being enteric coating layer(s).

The separating layer(s) can be applied to the core material by coating or layering
5 procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating process. As an alternative the separating layer(s) can be applied to the core material by using powder coating technique. The materials for the separating layers are pharmaceutically acceptable compounds such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone,
10 polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, water soluble salts of enteric coating polymers and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be
15 included into the separating layer(s).

When the optional separating layer, is applied to the core material it may constitute a variable thickness. The maximum thickness of the separating layer(s) is normally only limited by processing conditions. The separating layer may serve as a diffusion barrier and
20 may act as a pH-buffering zone. The pH-buffering properties of the separating layer(s) can be further strengthened by introducing into the layer(s) substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$,
25 $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$, aluminium hydroxide/sodium bicarbonate coprecipitate or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, carbonic, citric or other suitable, weak, inorganic or organic acids; or suitable organic bases, including basic amino acids and salts thereof. Talc or other
30 compounds may be added to increase the thickness of the layer(s) and thereby strengthen

the diffusion barrier. The optionally applied separating layer(s) is not essential for the invention. However, the separating layer(s) may improve the chemical stability of the active substance and/or the physical properties of the novel multiple unit tableted dosage form.

5

Alternatively, the separating layer may be formed in situ by a reaction between an enteric coating polymer layer applied on the core material and an alkaline reacting compound in the core material. Thus, the separating layer formed comprises a water soluble salt formed between the enteric coating layer polymer(s) and an alkaline reacting compound which is in the position to form a salt.

10

One or more enteric coating layers are applied onto the core material or onto the core material covered with separating layer(s) by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in suitable organic solvents. As enteric coating layer polymers one or more, separately or in combination, of the following can be used, e.g. solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating polymer(s).

15

The enteric coating layers contain pharmaceutically acceptable plasticizers to obtain the desired mechanical properties, such as flexibility and hardness of the enteric coating layers. Such plasticizers are for instance, but not restricted to triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or other plasticizers.

20

The amount of plasticizer is optimized for each enteric coating layer formula, in relation to selected enteric coating layer polymer(s), selected plasticizer(s) and the applied amount of said polymer(s), in such a way that the mechanical properties, i.e. flexibility and hardness of the enteric coating layer(s), for instance exemplified as Vickers hardness, are adjusted so

25

30

that the acid resistance of the pellets covered with enteric coating layer(s) does not decrease significantly during compression of pellets into tablets. The amount of plasticizer is usually above 10 % by weight of the enteric coating layer polymer(s), preferably 15 - 50 % and more preferably 20 - 50 %. Additives such as dispersants, colorants, pigments polymers
5 e.g. poly (ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be included into the enteric coating layer(s). Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acid susceptible material.

10 To protect the acid susceptible substance, the proton pump inhibitor, and to obtain an acceptable acid resistance of the dosage form according to the invention, the enteric coating layer(s) constitutes a thickness of approximately at least 10 μm , preferably more than 20 μm . The maximum thickness of the applied enteric coating is normally only limited by processing conditions.

15 Alternatively the enteric coating layer described above may be used for enteric coating layering of conventional tablets comprising a composition of an acid susceptible proton pump inhibitor and one or more antibacterial compounds, optionally covered by one of the separating layers described above. As a further alternative, the proton pump inhibitor may
20 be replaced in such a tablet by another gastric acid suppressing agents, such as a H_2 -receptor antagonist, for instance ranitidine, cimetidine or famotidine.

Over-coating layer

25 Pellets covered with enteric coating layer(s) may further be covered with one or more over-coating layer(s). The over-coating layer(s) can be applied to the enteric coating layered pellets by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating or layering process. The materials for over-coating layers are chosen among
30 pharmaceutically acceptable compounds such as, for instance sugar, polyethylene glycol,

polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such for instance magnesium stearate, titanium dioxide, talc and other additives may also be included into the over-coating layer(s). Said over-coating layer may further prevent potential agglomeration of enteric coating layered pellets, further it may protect the enteric coating layer towards cracking during the compaction process and enhance the tableting process. The maximum thickness of the applied over-coating layer(s) is normally only limited by processing conditions.

10

The above described over-coating layer may also be used as a tablet coating layer to obtain tablets of good appearance.

Antibacterial granulation

15

The active substance in the form of one or more antibacterial compounds is dry mixed with inactive excipients and the mixture is wet massed with a granulation liquid. The wet mass is dried preferably to a loss on drying of less than 3% by weight. Thereafter the dry mass is milled to a suitable size for the granules, such as smaller than 4 mm, and preferably smaller than 1 mm. Suitable inactive excipients for the antibacterial granulation are for instance, sodium starch glycolate, corn starch, crosslinked polyvinyl pyrrolidone, low substituted hydroxypropyl cellulose, microcrystalline cellulose and colloidal silicon dioxide anhydrous (Aerosil®). The dry mixture comprising antibacterial compound(s) is mixed with a suitable granulation liquid comprising for instance, polyvinyl pyrrolidone, hydroxypropyl cellulose, and optionally wetting agents, such as sodium lauryl sulphate, dissolved in purified water. Suitable lubricants for the tableting process are for instance, sodium stearyl fumarate, magnesium stearate and talc.

25

Multiple unit tablets

30

The enteric coating layered pellets comprising a proton pump inhibitor are mixed with the granules comprising antibacterial compounds and tablet excipients. The dry mixture is compressed into a multiple unit tableted dosage form. The compressed tablet is optionally covered with a filmforming agent(s) to obtain a smooth surface of the tablet and further
5 enhance the stability of the tablet during packaging and transport. Such a tablet coating layer may further comprise additives such as anti-tacking agents, colorants and pigments or other additives to obtain a tablet of good appearance.

The enteric coated pellets with or without an over-coat and the antibacterial granulation are
10 mixed with tablet excipients such as fillers, binders, disintegrants, lubricants and other pharmaceutically acceptable additives and compressed into tablets.

The amount of enteric coating layered pellets constitutes less than 75 % by weight of the total tablet weight and preferably less than 60 %. By choosing small enteric coating layered
15 pellets in the formulation according to the present invention, the number of pellets in each tablet can be held high which in turn makes the tablet divisible with retained dosing accuracy. Larger amount of the granulation comprising the antibacterial compound(s) may reduce the amount of enteric coating layered pellets in the multiple unit tableted dosage form.

20

Thus, the preferred multiple unit tablet formulation consists of enteric coating layered pellets containing one active substance in the form of an acid susceptible proton pump inhibitor, optionally mixed with alkaline reacting compound(s), compressed into tablet together with a granulation containing antibacterial compound(s) and optionally tablet
25 excipients. The addition of an alkaline reacting material to the proton pump inhibitor is not necessary, in any sense but such a substance may further enhance the stability of the proton pump inhibitor or some of the alkaline reacting compounds may react in situ with the enteric coating material to form a separating layer. The enteric coating layer(s) is making the pellets of the dosage form insoluble in acidic media, but disintegrating/dissolving in
30 near neutral to alkaline media such as, for instance the liquids present in the proximal part

of the small intestine, where dissolution of the proton pump inhibitor is desired. The antibacterial substance(s) may be released in the stomach. The enteric coating layered pellets may further be covered with an overcoating layer before being formulated into the tablet and they may also contain one or more separating layer(s) optionally containing
5 alkaline substance(s).

Process

The process for the manufacture of the dosage form represents a further aspect of the
10 invention. After formulation of the pellets by spray coating or layering of the proton pump inhibitor onto seeds, or by extrusion/spheronization or granulation, e.g. rotor granulation of homogeneous pellets, the pellets are first optionally covered with the separating layer(s) and then with the enteric coating layer(s) or a separating layer is spontaneously developed in situ between an alkaline core material and the enteric coating layer material. The coating
15 is carried out as described above and in the accompanying examples. The preparation of the granulation comprising the antibacterial compound(s) is also described above and in the examples. The pharmaceutical processes can preferably be completely water-based.

The enteric coating layered pellets, with or without an over-coat, are mixed with the
20 prepared granules, tablet excipients and other pharmaceutical acceptable additives and compressed into tablets. The tablet may be in the form of a two layer tablet, wherein one layer comprises the enteric coating layered pellets optionally mixed with inactive excipients and the other layer comprises the prepared granules of the antibacterial substance(s). Alternatively, the different active substances in the form of powders may be
25 intimately dry mixed with tablet excipients, wet massed and compressed into conventional tablets before applying an optional separating layer and an enteric coating layer. The tablet may be in the form of a two layer enteric coating layered tablet, wherein one layer comprises one of the active substances and the other layer comprises the other active substance(s). As a further alternative, the proton pump inhibitor in the form of enteric

coating layered pellets may be filled in a capsule together with the antibacterial substance(s) in the form of a granulation optionally mixed with pharmaceutical excipients.

Use of the preparation

5

The dosage forms according to the invention are especially advantageous in the treatment of *H. pylori* infections. They are administered one to several times a day, preferably once or twice daily. The typical daily dose of the active substances varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general each dosage form will comprise 0,1-200 mg of the proton pump inhibitor and 0,1 mg - 1,2 g of the antibacterial compound(s). Preferably, each dosage form will comprise 10-80 mg of the proton pump inhibitor and 100-900 mg of the antibacterial compound(s), and more preferably 20-40 mg of proton pump inhibitor and 250-650 mg of the antibacterial compound(s), respectively.

15

The multiple unit tablet preparation is also suitable for dispersion in an aqueous liquid with neutral or slightly acidic pH-value before being orally administered or fed through a nasogastric tube.

20

The invention is illustrated more in detail in the following examples.

Examples

Example 1:

25

Multiple unit dosage form comprising omeprazole and metronidazole (batch size 10.000 tablets).

Core material

30

Magnesium omeprazole

12.00 kg

	Sugar sphere seeds	12.00 kg
	Hydroxypropyl methylcellulose	1.8 kg
	Water purified	35.4 kg
5	<u>Separating layer</u>	
	Core material (acc. to above)	23.50 kg
	Hydroxypropyl cellulose	2.35 kg
	Talc	4.03 kg
	Magnesium stearate	0.34 kg
10	Water purified	48.00 kg
	<u>Enteric coating layer</u>	
	Pellets covered with separating layer (acc. to above)	29.00 kg
	Methacrylic acid copolymer (30% suspension)	38.70 kg
15	Triethyl citrate	3.48 kg
	Mono- and diglycerides (NF)	0.58 kg
	Polysorbate 80	0.06 kg
	Water purified	22.68 kg
20	<u>Over-coating layer</u>	
	Enteric coating layered pellets (acc. to above)	44.7 kg
	Hydroxypropyl methylcellulose	0.58 kg
	Water purified	11.6 kg
25	<u>Tablets</u>	
	Prepared pellets comprising omeprazole as prepared above	933 g
	Metronidazole	4000 g
	Sodium starch glycolate	500 g
	Aerosil®	25 g
30	Sodium lauryl sulphate	20 g

Polyvidone K90	253.1 g
Microcrystalline cellulose	1181 g
Water purified	2278 g
Sodium stearyl fumarate	66.5 g

5

Tablet coating solution (for 10 kg tablets)

Hydroxypropyl methylcellulose	250 g
Polyethylene glycol 6000	62.5 g
Titanium dioxide	62.5 g
Water purified	2125 g
Hydrogen pyroxide	0.75 g

10

Suspension layering is performed in a fluid bed apparatus. Magnesium omeprazole is sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder.

15

The size of sugar sphere seeds are in the range of 0.25 to 0.35 mm.

The prepared core material is covered with a separating layer in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethyl citrate and polysorbate is sprayed onto the pellets covered with a separating layer in a fluid bed apparatus. In a fluid bed apparatus enteric coating layered pellets are coated with hydroxypropyl methylcellulose solution. The over-coating layered pellets are classified by sieving.

20

Sodium lauryl sulphate and polyvidone K90 are dissolved in purified water to form the granulation liquid. Metronidazole, sodium starch glycolate and Aerosil® are dry-mixed. The granulating liquid is added to the powder mixture and the mass is wet-mixed. The wet mass is dried in a steamoven at 50°C. The prepared granulation is milled through sieve 1 mm in an oscillating mill equipment.

25

The enteric coating layered pellets with an over-coating layer, prepared granules, microcrystalline cellulose and sodium stearyl fumarate are mixed and compressed into tablets using a rotary tableting machine equipped with 8.5x17 mm oval punches. The amount of omeprazole in each tablet is approx. 20 mg and the amount of metronidazole is approx. 400 mg. Tableting speed is set to 50 rpm and the upper punch force is set to 20 kN. Tablet hardness measured is 150-164N.

The obtained tablets are covered with a conventional tablet coating layer.

10 Example 2:

Multiple unit dosage form comprising omeprazole and clarithromycin (batch size 10.000 tablets).

15 Tablets

Enteric coating layered pellets with an over-coating layer (manufacturing and composition as in example 1)	978 g
Clarithromycin	2500 g
Microcrystalline cellulose	3000 g
20 Sodium starch glycolate	350 g
Aerosil®	40 g
Sodium lauryl sulphate	12.5 g
Polyvidone K90	384.8 g
Water purified	3463 g
25 Magnesium stearate	105 g

Tablet coating solution (for 10 kg tablets)

Hydroxypropyl methylcellulose	250 g
Polyethylene glycol 6000	62.5 g
30 Titanium dioxide	62.5 g

Water purified	2125 g
Hydrogen pyroxide	0.75 g

Sodium lauryl sulphate and polyvidone K90 are dissolved in purified water to form the granulation liquid. Clarithromycin, microcrystalline cellulose, sodium starch glycolate and Aerosil® are dry-mixed. The granulating liquid is added to the powder mixture and the mass is wet-mixed. The wet mass is dried in a steam-oven. The prepared granulation is milled through sieve 1 mm in an oscillating mill equipment.

The enteric coating layered pellets with an over- coating layer, prepared granules and magnesium stearate are mixed and compressed into tablets as in example 1. The amount of omeprazole in each tablet is approx. 20 mg and the amount of clarithromycin is approx. 250 mg. Tableting speed is set to 50 rpm and the upper punch force is set to 14kN. Tablet hardness measured is 178-189N.

The obtained tablets are covered with a conventional tablet coating layer.

Example 3:

Multiple unit dosage form comprising omeprazole and clarithromycin (batch size 10.000 tablets).

Tablets

Enteric coating layered pellets with an over-coating layer (manufacturing and composition as in example 1)	978 g
Clarithromycin	5000 g
Microcrystalline cellulose	2500 g
Sodium starch glycolate	350 g
Aerosil®	40 g
Sodium lauryl sulphate	25 g

	Polyvidone K90	361.9 g
	Water purified	3257 g
	Magnesium stearate	91.7 g
5	<u>Tablet coating solution (for 10 kg tablets)</u>	
	Hydroxypropyl methylcellulose	250 g
	Polyethylene glycol 6000	62.5 g
	Titanium dioxide	62.5 g
	Water purified	2125 g
10	Hydrogen pyroxide	0.75 g

The antibacterial granulation is manufactured as in example 2. Enteric coating layered pellets with an over-coating layer, prepared granules and magnesium stearate are mixed and compressed into tablets using a rotary tableting machine equipped with 10x21 mm oval punches. The amount of omeprazole in each tablet is approx. 20 mg and the amount of clarithromycin is approx. 500 mg. Tableting speed is set to 50 rpm and the upper punch force is set to 20kN. Tablet hardness measured is 105-128N.

The obtained tablets are covered with a conventional tablet coating layer.

20

Example 4:

Multiple unit dosage form comprising, metronidazole and clarithromycin (batch size 2.500 tablets).

25

Core material

	Magnesium omeprazole	15.00 kg
	Sugar sphere seeds	15.00 kg
	Hydroxypropyl methylcellulose	2.25 kg
30	Water purified	40.25 kg

Separating layer

	Core material (acc. to above)	15.00 kg
	Hydroxypropyl cellulose	1.5 kg
5	Talc	2.57 kg
	Magnesium stearate	0.21 kg
	Water purified	30.00 kg

Enteric coating layer

10	Pellets covered with separating layer (acc. to above)	18.00 kg
	Methacrylic acid copolymer (30% suspension)	30.00 kg
	Triethyl citrate	2.7 kg
	Mono- and diglycerides (NF)	0.49 kg
	Polysorbate 80	0.05 kg
15	Water purified	19.00 kg

Tablets

	Enteric coating layered pellets (acc. to above)	246 g
	Clarithromycin	625 g
20	Metronidazole	1000 g
	Microcrystalline cellulose	375 g
	Sodium starch glycolate	125 g
	Aerosil®	10 g
	Sodium lauryl sulphate	8 g
25	Polyvidone K90	117.8 g
	Water purified	1060 g
	Sodium stearyl fumarate	48.2 g

Suspension layering is performed in a fluid bed apparatus. Magnesium omeprazole is
 30 sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder.

The prepared core material is covered with a separating layer in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethyl
5 citrate and polysorbate is sprayed onto the pellets covered with a separating layer in a fluid bed apparatus. The enteric coating layered pellets are classified by sieving.

Sodium lauryl sulphate and polyvidone K90 are dissolved in purified water to form the granulation liquid. Clarithromycin, metronidazole, microcrystalline cellulose, sodium
10 starch glycolate and Aerosil are dry-mixed. The granulating liquid is added to the powder mixture and the mass is wet-mixed. The wet mass is dried in a steam-oven. The prepared granulation is milled through sieve 1 mm in an oscillating mill equipment.

Enteric coating layered pellets, prepared granules and sodium stearyl fumarate are mixed
15 and compressed into tablets as in example 3. The amount of omeprazole in each tablet is approx. 20 mg, the amount of metronidazole is 400 mg and the amount of clarithromycin is 250 mg. Tableting speed is set to 50 rpm and the upper punch force is set to 24 kN. Tablet hardness measured is 130-142N.

20 Example 5:

Multiple unit dosage form comprising lansoprazole and clarithromycin (batch size 1.000 tablets).

25 Core material

Lansoprazole	400 g
Sugar sphere seeds	400 g
Hydroxypropyl methylcellulose	80 g
Water purified	1200 g

Separating layer

	Core material (acc. to above)	400 g
	Hydroxypropyl cellulose	40 g
	Talc	69 g
5	Magnesium stearate	6 g
	Water purified	800 g

Enteric coating layer

	Pellets covered with a separating layer (acc. to above)	400 g
10	Methacrylic acid copolymer (30% suspension)	667 g
	Triethyl citrate	60 g
	Mono- and diglycerides (NF)	10 g
	Polysorbate 80	1 g
	Water purified	391 g

15

Tablets

	Enteric coating layered pellets (acc. to above)	89.8 g
	Clarithromycin	250 g
	Microcrystalline cellulose	300 g
20	Sodium starch glycolate	35 g
	Aerosil®	4 g
	Sodium lauryl sulphate	1.25 g
	Polyvidone K90	45.2 g
	Water purified	406.8 g
25	Magnesium stearate	10.1 g

Suspension layering is performed in a fluid bed apparatus. Lansoprazole is sprayed onto the sugar sphere seeds from a suspension containing the dissolved binder in a water solution.

Pellets covered with separating layer and enteric coating layer are produced as in example

30 1. The antibacterial granulation is manufactured as in example 2.

Enteric coating layered pellets, prepared granules and magnesium stearate are mixed and compressed into tablets using a rotary tableting machine equipped with 8.5x17 mm oval punches. The amount of lansoprazole in each tablet is approx. 20 mg and the amount of clarithromycin is approx. 250 mg. The upper punch force is set to 5.8 kN , and the tablet hardness is measured 63N.

Example 6.

Multiple unit dosage form comprising (s)-omeprazole magnesium salt, metronidazole and clarithromycin (batch size 200 tablets).

Core material

(s)-Omeprazole magnesium salt	120 g
Sugar sphere seeds	150 g
Hydroxypropyl methylcellulose	18 g
Polysorbate 80	2.4 g
Water purified	562 g

Separating layer

Core material (acc. to above)	200 g
Hydroxypropyl cellulose	30 g
Talc	51.4 g
Magnesium stearate	4.3 g
Water purified	600 g

Enteric coating layer

Pellets covered with separating layer (acc. to above)	250 g
Methacrylic acid copolymer (30% suspension)	333.7 g
Triethyl citrate	30 g

Mono- and diglycerides (NF)	5 g
Polysorbate 80	0.5 g
Water purified	196 g

5 Metronidazole and clarithromycin granulation

Clarithromycin	3500 g
Metronidazole	5600 g
Microcrystalline cellulose	1400 g
Sodium starch glycolate	700 g
10 Aerosil®	56 g
Polyvidon K90	511 g
Water purified	4600 g

Tablets

15 Pellets comprising (s)-omeprazole Mg-salt (acc. to above)	25.5 g
Granulation comprising clarithromycin and metronidazole (acc. to above)	168.1 g
Microcrystalline cellulose	40 g
Sodium stearyl fumarate	4.7 g

20

Tablet coating solution (for 10kg tablets)

Hydroxypropyl methylcellulose	250 g
Polyethylene glycol 6000	62.5 g
Titanium dioxide	62.5 g
25 Water purified	2125 g
Hydrogen pyroxide	0.75 g

Suspension layering is performed in a fluid bed apparatus. (s)-Omeprazole magnesium salt is sprayed onto sugar sphere seedes from a water suspension containing the dissolved

binder and polysorbate 80. The size of sugar sphere seeds are in the range of 0.25 to 0.35 mm.

The prepared core material is covered with a separating layer in a fluid bed apparatus with hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethyl citrate and polysorbate is sprayed onto the pellets covered with a separating layer in a fluid bed apparatus. The enteric coating layered pellets are classified by sieving.

Polyvidone K90 is dissolved in purified water to form the granulation liquid. Clarithromycin, metronidazole, microcrystalline cellulose, sodium starch glycolate and Aerosil[®] are dry-mixed. The granulating liquid is added to the powder mixture and the mass is wet-mixed. The wet mass is dried in a steam-oven. The prepared granulation is milled through sieve 1mm in an oscillating mill equipment.

The enteric coating layered pellets, prepared granules, microcrystalline cellulose and magnesium stearate are mixed and compressed into tablets on a tableting machine equipped with 10x21 mm oval punches. The amount of (s)-omeprazole is approx. 20 mg, the amount of metronidazole is approx. 400 mg and the amount of clarithromycin is approx. 250 mg. Tablet hardness tested with a Schleuniger apparatus was 140-150N.

20

The obtained tablets are covered with a conventional tablet coating layer.

The results from tests on acid resistance of the compressed tablets are disclosed in Table 1, below.

25

Table 1

Example No	Acid resistance, tablets (%), n=3
------------	--------------------------------------

30

1

95

	2	99
	3	91
	4	92
	5	90
5	6	93

Example 7:

An enteric coating layered tablet comprising magnesium omeprazole, clarithromycin and
 10 metronidazol (batch size 1.000 tablets).

Tablets

	Magnesium omeprazole	20 g
	Clarithromycin	250 g
15	Metronidazole	400 g
	Microcrystalline cellulose	150 g
	Sodium starch glycolate	50 g
	Aerosil®	4 g
	Sodium lauryl sulphate	3.2 g
20	Polyvidone K90	50 g
	Water purified	450 g
	Sodium stearyl fumarate	18 g

Solution for separating layer (for 10 kg tablets)

25	Hydroxypropyl methylcellulose	300 g
	Hydrogen peroxide (30%)	0.003 g
	Water purified	2700 g

Solution for enteric coating layer (for 10 kg tablets)

30	Methacrylic acid copolymer dispersion (30%)	2450 g
----	---	--------

Polyethylene glycol 400	80 g
Titanium dioxide	100 g
Water purified	1960 g

- 5 Sodium lauryl sulphate and polyvidone K90 are dissolved in purified water to form the granulation liquid. Magnesium omeprazole, clarithromycin, metronidazole, microcrystalline cellulose, sodium starch glycolate and Aerosil® are dry-mixed. The granulating liquid is added to the powder mixture and the mass is wet-mixed. The wet mass is dried in a steam-oven. The prepared granulation is milled through sieve 1 mm in an
10 oscillating mill equipment.

The prepared granules and sodium stearyl fumarate are mixed and compressed into tablets using a rotary tableting machine equipped with 8.5x19 mm oval punches. The amount of omeprazole in each tablet is 20 mg, the amount of clarithromycin is 250 mg and the
15 amount of metronidazole is 400 mg.

The obtained tablets are covered with a separating layer and an enteric tablet coating layer.

Example 8:

20

An enteric coating layered tablet comprising lansoprazole and clarithromycin (batch size 1.000 tablets).

Tablets

25	Lansoprazole	20 g
	Clarithromycin	250 g
	Microcrystalline cellulose	150 g
	Sodium starch glycolate	50 g
	Aerosil®	4 g
30	Sodium lauryl sulphate	3.2 g

Polyvidone K90	50 g
Water purified	450 g
Sodium stearyl fumarate	18 g

5 Solution for separating layer (for 10kg tablets)

Hydroxypropyl methylcellulose	300 g
Hydrogen peroxide (30%)	0.003 g
Water purified	2700 g

10 Solution for enteric coating layer (for 10 kg tablets)

Methacrylic acid copolymer dispersion (30%)	2450 g
Polyethylene glycol 400	80 g
Titanium dioxide	100 g
Water purified	1960 g

15

Sodium lauryl sulphate and polyvidone K90 are dissolved in purified water to form the granulation liquid. Lansoprazole, clarithromycin, microcrystalline cellulose, sodium starch glycolate and Aerosil® are dry- mixed. The granulating liquid is added to the powder mixture and the mass is wet-mixed. The wet mass is dried in a steam-oven. The prepared granulation is milled through sieve 1 mm in an oscillating mill equipment.

20

The prepared granules and sodium stearyl fumarate are mixed and compressed into tablets using a rotary tableting machine equipped with 8.5x19 mm oval punches. The amount of lansoprazole in each tablet is 20 mg, the amount of clarithromycin is 250 mg.

25

The obtained tablets are covered with a separating layer and an enteric tablet coating layer.

Example 9:

30 A capsule formulation comprising omeprazole and metronidazol.

Core material

	Magnesium omeprazole	10.00 kg
	Sugar sphere seeds	10.00 kg
5	Hydroxypropyl methylcellulose	1.5 kg
	Water purified	29.65 kg

Separating layer

	Core material (acc. to above)	20.00 kg
10	Hydroxypropyl cellulose	2.00 kg
	Talc	3.43 kg
	Magnesium stearate	0.29 kg
	Water purified	40.00 kg

15 Enteric coating layer

	Pellets covered with a separating layer (acc. to above)	24.00 kg
	Methacrylic acid copolymer (30% suspension)	40.00 kg
	Triethyl citrate	3.6 kg
	Mono- and diglycerides (NF)	0.6 kg
20	Polysorbate 80	0.06 kg
	Water purified	24.45 kg

Metronidazole granulation

	Metronidazole	5000 g
25	Polyvidone K90	62.6 g
	Water purified	562.9 g

Polyvidon K90 is dissolved in purified water to form the granulation liquid. The liquid is added to metronidazole and the mass is wet-mixed. The wet mass is dried in a steam oven.

30 The prepared granulation is milled through sieve 1 mm in an oscillating mill equipment.

Capsules

Metronidazole granulation (acc. to above)	1250.8 g
Enteric coating layered pellets (acc. to above)	104 mg/capsule
5 (manufacturing as in Example 4)	
Magnesium stearate	24.8 g

The metronidazole granulation is mixed with magnesium stearate. Prepared granules and enteric coating layered pellets are filled into capsules, size 0, using a capsule filling
10 machine equipped with powder dosing unit and pellet filler. The amount of omeprazole in each capsule is 20 mg and the amount of metronidazole is 400 mg. Capsule filling speed is set to 61 rpm.

Example 10:

15

A capsule formulation comprising omeprazole and clarithromycin.

Core material

Magnesium omeprazole	15.00 kg
20 Sugar sphere seeds	15.00 kg
Hydroxypropyl methylcellulose	2.25 kg
Water purified	44.00 kg

Separating layer

25 Core material (acc. to above)	30.00 kg
Hydroxypropyl cellulose	3.00 kg
Talc	5.14 kg
Magnesium stearate	0.43 kg
Water purified	60.00 kg

Enteric coating layer

	Pellets covered with a separating layer (acc. to above)	750 g
	Methacrylic acid copolymer	322.5 g
	Triethyl citrate	96.8 g
5	Mono- and diglycerides (NF)	16.1 g
	Polysorbate 80	1.61 g
	Water purified	631.4 g

Over-coating layer

10	Hydroxypropyl methylcellulose	22.5 g
	Water purified	427.5 g

Clarithromycin granulation

	Clarithromycin	5000 g
15	Ethanol (99.5%)	2064 g
	Sodium lauryl sulphate	50 g

Sodium lauryl sulphate is dissolved in ethanol to form the granulation liquid. The liquid is added to clarithromycin and the mass is wet-mixed. The wet mass is dried in a steam oven.

20 The prepared granulation is milled through sieve 1 mm in an oscillating mill equipment.

Capsules

	Clarithromycin granulation (acc. to above)	1500 g
	Hydroxypropyl cellulose (L-HPC)	75 g
25	Magnesium stearate	31.5 g
	Pellets covered with an overcoating layer (acc. to above and manufacturing as in example 1)	96.7 mg/capsule

The clarithromycin granulation is mixed with L-HPC and magnesium stearate and capsules of size 00 is filled as in example 8. The amount of omeprazole in each capsule is 20 mg and the amount of clarithromycin is 500 mg.

5 Example 11:

A capsule formulation comprising omeprazole, clarithromycin and metronidazole.

Capsules

10	Clarithromycin granulation	1805 g
	(manufacturing and composition as in example 9)	
	Hydroxypropyl cellulose (L-HPC)	90.3 g
	Metronidazole	2670 g
	Magnesium stearate	91.3 g
15	Pellets covered with an overcoating layer	96.7 mg/capsule
	(manufacturing and composition as example 1)	

The clarithromycin granulation is mixed with metronidazole, L-HPC and magnesium stearate. Capsules of size 00 is filled as in example 8. The amount of omeprazole in each capsule is 20 mg, the amount of metronidazole is 400 mg and the amount of clarithromycin is 250 mg.

Example 12:

25 A dosage form comprising lansoprazole and clarithromycin, filled into capsules in the form of granules.

Core material

	Lansoprazole	400 g
	Sugar sphere seeds	400 g
30	Hydroxypropyl methylcellulose	80 g

	Water purified	1200 g
	<u>Separating layer</u>	
	Core material (acc. to above)	400 g
5	Hydroxypropyl cellulose	40 g
	Talc	69 g
	Magnesium stearate	6 g
	Water purified	800 g
10	<u>Enteric coating layer</u>	
	Pellets covered with separating layer (acc. to above)	400g
	Methacrylic acid copolymer (30% suspension)	667 g
	Triethyl citrate	60 g
	Mono- and diglycerides (NF)	10 g
15	Polysorbate 80	1 g
	Water purified	391 g
	<u>Clarithromycin granulation</u>	
	Clarithromycin	5000 g
20	Ethanol (99.5%)	2064 g
	Sodium lauryl sulphate	50 g
	Sodium lauryl sulphate is dissolved in ethanol to form the granulation liquid. The liquid is added to clarithromycin and the mass is wet-mixed. The wet mass is dried in a steam oven.	
25	The prepared granulation is milled through sieve 1mm in an oscillating mill equipment.	
	<u>Capsules</u>	
	Clarithromycin granulation (acc. to above)	1500 g
	Hydroxypropyl cellulose (L-HPC)	75 g
30	Magnesium stearate	31.5 g

Enteric coating layered pellets (acc. to above and 94 mg/capsule
manufacturing as in example 5)

The clarithromycin granulation is mixed with L-HPC and magnesium stearate and capsules
5 of size 00 is filled as in example 8. The amount of lansoprazole in each capsule is 20 mg
and the amount of clarithromycin is 500 mg.

The best mode to carry out the invention are dosage forms of the compositions described in
Examples 3, 4 and 6.

10

The enteric coating layered pellets and other intermediate products used in the
compositions described above, may also be prepared as described in the following
examples.

15 Example 13

Preparation of enteric coating layered pellets by extrusion/spheronization.

Core material

20	Magnesium omeprazole	600 g
	Mannitol	1000 g
	Microcrystalline cellulose	300 g
	Hydroxypropyl cellulose	100 g
	Sodium lauryl sulphate	6 g
25	Water purified	802 g

Separating layer

	Core material (acc. to above)	400 g
	Hydroxypropyl methylcellulose	48 g
30	Water purified	960 g

Enteric coating layer

- | | | |
|---|---|-------|
| | Pellets covered with separating layer (acc. to above) | 200 g |
| | Methacrylic acid copolymer | 100 g |
| 5 | Triethyl citrate | 30 g |
| | Mono- and diglycerides (NF) | 5 g |
| | Polysorbate 80 | 0.5 g |
| | Water purified | 309 g |
- 10 Sodium lauryl sulphate is dissolved in purified water to form the granulation liquid. Magnesium omeprazole, mannitol, microcrystalline cellulose and hydroxypropyl cellulose are dry-mixed. The granulation liquid is added to the powder mixture and the mass is wet-mixed.
- 15 The wet mass is forced through an extruder equipped with screens of size 0.5 mm. The extrudate is spheronized on a friction plate in a spheronizing apparatus. The core material is dried in a fluid bed dryer and classified. The prepared core material is covered by a separating layer in a fluid bed apparatus with a hydroxypropyl methylcellulose/water solution.
- 20 The enteric coating layer is applied to the pellets covered with separating layer from an aqueous dispersion of methacrylic acid copolymer plasticized with triethyl citrate to which a mono- and diglycerides/polysorbate dispersion has been added. The pellets are dried in a fluid bed apparatus.

Example 14

Preparation of enteric coating layered pellets by powder.

5 Core material

Magnesium omeprazole	1 500 g
Sugar sphere seeds	1 500 g
Hydroxypropyl methylcellulose	420 g
Aerosil®	8 g
10 Water purified	4 230 g

Separating layer

Core material (acc. to above)	500 g
Hydroxypropyl cellulose	40 g
15 Talc	67 g
Magnesium stearate	6 g
Water purified	800 g

Enteric coating layer

20 Pellets covered with separating layer (acc. to above)	500 g
Methacrylic acid copolymer	200 g
Triethyl citrate	60 g
Water purified	392 g

- 25 Magnesium omeprazole, part of the hydroxypropyl methylcellulose and Aerosil® are dry-mixed forming a powder. Sugar sphere seeds (0.25-0.40 mm) are layered with the powder in a centrifugal fluidized coating granulator while spraying a hydroxypropyl methylcellulose solution (6 %, w/w).

The prepared core material is dried and covered by a separating layer in a centrifugal fluidized coating-granulator. A fluid bed apparatus is used for enteric coating layering.

Example 15

5

Preparation of enteric coating layered pellets with silicon dioxide seeds.

Core material

	Magnesium omeprazole	8.00 kg
10	Silicon dioxide	8.00 kg
	Hydroxypropyl methylcellulose	1.41 kg
	Sodium lauryl sulphate	0.08 kg
	Water purified	28.00 kg

15 Separating layer

	Core material (acc. to above)	10.00 kg
	Hydroxypropyl methylcellulose	0.80 kg
	Water purified	10.00 kg

20 Enteric coating layer

	Pellets covered with separating layer (acc. to above)	300 g
	Methacrylic acid copolymer	124 g
	Polyethylene glycol 400	25 g
	Mono- and diglycerides (NF)	3 g
25	Polysorbate 80	1 g
	Water purified	463 g

Suspension layering is performed in a fluid bed apparatus. Magnesium omeprazole is sprayed onto the silicon dioxide seeds from a water suspension containing the dissolved
30 binder and a surface active ingredient.

The prepared core material is covered with a separating layer in a fluid bed apparatus with a hydroxypropyl methylcellulose solution. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, polyethylene glycol 400 and polysorbate is sprayed onto the pellets covered with separating layer in a fluid bed apparatus.

Example 16

Preparation of enteric coating layered pellets.

Enteric coating layer

Pellets covered with separating layer
(manufacturing and composition
as in example 13)

500 g

Methacrylic acid copolymer

250 g

Polyethylene glycol 6000

75 g

Mono- and diglycerides (NF)

12.5 g

Polysorbate 80

1.2 g

Water purified

490 g

Example 17

Preparation of enteric coating layered pellets.

Enteric coating

Pellets covered with separating layer

500 g

(manufacturing and composition as in example 1)

Hydroxypropyl methylcellulose phthalate

250 g

Cetanol

50 g

Ethanol (95%)

1000 g

Acetone	2500 g
---------	--------

Example 18

- 5 Preparation of enteric coating layered pellets.

Core material

	Omeprazole	225 g
	Mannitol	1425 g
10	Hydroxypropyl cellulose	60 g
	Microcrystalline cellulose	40 g
	Lactose anhydrous	80 g
	Sodium lauryl sulphate	5 g
	Disodium hydrogen phosphate dihydrate	8 g
15	Water purified	350 g

Separating layer

	Core material (acc. to above)	300 g
	Hydroxypropyl cellulose	30 g
20	Talc	51 g
	Magnesium stearate	4 g

Enteric coating layer

	Pellets covered with separating layer (acc. to above)	300 g
25	Methacrylic acid copolymer	140 g
	Triethyl citrate	42 g
	Mono- and diglycerides (NF)	7 g
	Polysorbate 80	0.7 g

The dry ingredients for producing the core material are well mixed in a mixer. Addition of granulation liquid is made and the mixture is kneaded and granulated to a proper consistency. The wet mass is pressed through an extruder screen and the granules are converted into a spherical form in a spheronizer. The core material is dried in a fluid bed apparatus and classified into a suitable particle size range, e.g. 0.5 - 1.0 mm. The prepared core material is covered with a separating layer and enteric coating layered as described in previous examples.

Preparation of active substance.

10

Magnesium omeprazole used in the examples is produced according to the process described in WO/SE94/00680, omeprazole is produced according to the process disclosed in EP-A1 0005129, and the single enantiomers of omeprazole salts are produced as described in WO/SE94/00509. These documents are hereby incorporated in a whole by reference.

15

CLAIMS

1. An oral pharmaceutical dosage form comprising an acid susceptible proton pump inhibitor together with at least one antibacterial compound and optionally pharmaceutically acceptable excipients, characterized in that the dosage form is in the form of a fixed unit dosage form comprising at least two pharmaceutically active components.
2. A dosage form according to claim 1, wherein the dosage form is a tablet formulation.
3. A dosage form according to claim 1, wherein the dosage form is a capsule formulation.
4. A dosage form according to claim 1, wherein the dosage form comprises an acid susceptible proton pump inhibitor and two antibacterial compounds.
5. A dosage form according to claim 1, wherein the proton pump inhibitor is omeprazole or its single enantiomers or an alkaline salt thereof.
6. A dosage form according to claim 1, wherein the proton pump inhibitor is (s)-omeprazole magnesium salt.
7. A dosage form according to claim 1, wherein the proton pump inhibitor is lansoprazole.
8. A dosage form according to any of claims 5 - 7, wherein the antibacterial compound is clarithromycin and/or metronidazole.
9. A dosage form according to any of claims 5 - 7, wherein the antibacterial compound is amoxicillin and/or clarithromycin or metronidazole.

10. A dosage form according to claim 1, wherein the amount of proton pump inhibitor is in the range of 10-80 mg and the amount of antibacterial compound(s) is in the range of 100-900 mg.

5 11. A dosage form according to claim 1, wherein the amount of proton pump inhibitor is in the range of 20-40 mg and the amount of antibacterial compound(s) is in the range of 250-650 mg.

12. A tableted dosage form according to claim 2, wherein the dosage form consists of
10 two separate layers, each one comprising different active substance(s).

13. A tableted dosage form according to claim 2, wherein the tablet formulation is a multiple unit tableted dosage form comprising the acid susceptible proton pump inhibitor in the form of individually enteric coating layered pellets compressed together with an
15 antibacterial granulation into a tablet, whereby the enteric coating layer covering the individual pellets has mechanical properties such that the tableting of the pellets together with the antibacterial granulation and optionally pharmaceutically acceptable excipients does not significantly affect the acid resistance of the individually enteric coating layered pellets.

20

14. A tableted dosage form according to claim 13, wherein the acid resistance of the individually enteric coating layered pellets is in coherence with the requirements on enteric coating layered articles defined in the United States Pharmacopeia.

25 15. A tableted dosage form according to 13, wherein the acid resistance of the individually enteric coating layered pellets does not decrease more than 10 % during the compression of the individual pellets into the multiple unit tableted dosage form.

30 16. A tableted dosage form according to claim 13, wherein the enteric coating of the individual pellets comprises a plasticized enteric coating layer material.

17. A tableted dosage form according to claim 13, wherein the individually enteric coating layered pellets are further covered with an over-coating layer comprising pharmaceutically acceptable excipients.

5

18. A tableted dosage form according to claim 13, wherein the enteric coating layered pellets consist of a seed layered with the proton pump inhibitor.

19. A tableted dosage form according to claim 13, wherein the tablet is divisible.

10

20. A tableted dosage form according to claim 19, wherein the tablet is dispersible to a suspension of individually enteric coating layered pellets in an aqueous liquid.

21. A tableted dosage form according to claim 2, wherein the tablet is an enteric coating layered tablet, optionally with a separating layer under the enteric coating layer and the tablet comprises at least two different pharmaceutically active substances in admixture with each other.

15

22. A process for the manufacture of a fixed dosage form comprising an acid susceptible proton pump inhibitor and one or more antibacterial compounds in a capsule, characterized in that the proton pump inhibitor is prepared in the form of individually enteric coating layered pellets and the pellets are filled into a capsule together with the antibacterial compound(s) optionally mixed with pharmaceutically acceptable excipients.

20

23. A process for the manufacture of a fixed dosage form comprising an acid susceptible proton pump inhibitor and one or more antibacterial compounds in a multiple unit tableted dosage form, characterized in that the proton pump inhibitor is prepared in the form of individually enteric coating layered pellets and these pellets are mixed with a prepared antibacterial granulation and optionally pharmaceutically acceptable tablets excipients whereafter the dry mixture is compressed into a multiple unit tablet without

25

30

giving any significant change of the acid resistance of the enteric coating layer covering the individually enteric coating layered pellets.

24. A process for the manufacture of a fixed dosage form comprising an acid
5 susceptible proton pump inhibitor and one or more antibacterial compound(s) in an enteric coating layered tablet characterized in that the proton pump inhibitor is admixed with the antibacterial compound(s) and pharmaceutically acceptable excipients whereafter the dry mixture is compressed into a tablet, which tablet is covered with an enteric coating layer and optionally a separating layer is applied onto the tablet before the enteric coating layer.

10

25. A dosage form according to any of claims 1 to 21 for use in the treatment of disorders associated with *Helicobacter* infections in mammals and man.

26. A dosage form according to claim 25, wherein the disorder is a gastric disorder
15 associated with *Helicobacter pylori* infections.

27. A method for the treatment of disorders associated with *Helicobacter* infections in mammals and man by administering to a host in need thereof a therapeutically effective dose of a multiple unit tableted dosage form according to any of claims 1 to 21.

20

28. A method according to claim 27, wherein the disorder is a gastric disorder associated with *Helicobacter pylori* infections.

29. Use of a dosage form according to any of claims 1 to 21 for the manufacture of a
25 medicament for the treatment of disorders associated with *Helicobacter* infections in mammals and man.

30. Use of a dosage form according to claim 29, wherein the disorder is a gastric disorder associated with *Helicobacter pylori* infections.

Fig. 1

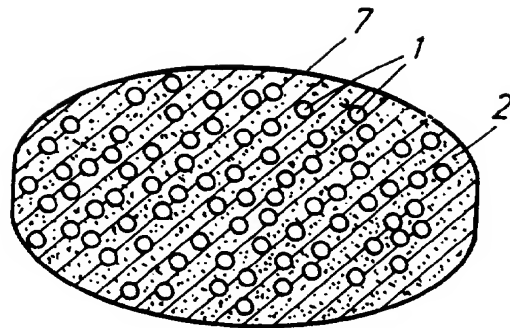


Fig. 2

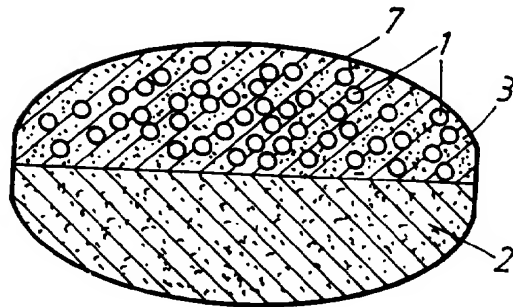


Fig. 3

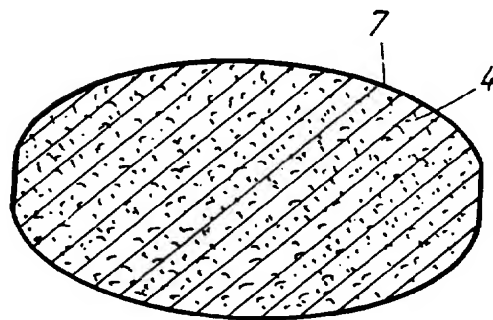
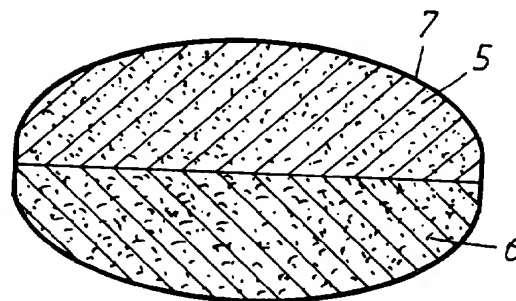


Fig. 4



INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/00125

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 45/06, A61K 31/44, A61K 31/71, A61K 31/41, A61K 31/43, A61K 9/20, A61K 9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, WPIL, USFULLTEXT, CLAIMS, EMBASE, MEDLINE, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP 0642797 A1 (TAKEDA CHEMICAL INDUSTRIES, LTD.), 15 March 1995 (15.03.95) --	1-26
Y	WO 9211849 A1 (THE PROCTER & GAMBLE COMPANY), 23 July 1992 (23.07.92), page 3, line 24 - line 32; page 7, line 22 - line 24 --	1-26
Y	Dialog Information Services, File 73, EMBASE, Dialog accession no. 9150953, EMBASE accession no. 94095444, Logan R.P.H. et al: "Eradication of Helicobacter pylori with clarithromycin and omeprazole", GUT (United Kingdom), 1994, 35/3 (323-326) --	1-26

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search

9 May 1996

Date of mailing of the international search report

10 -05- 1996

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/00125

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0365947 A1 (PHARMACIA AB), 2 May 1990 (02.05.90) -- -----	1-26

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/00125

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 27-30
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/00125

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP-A1-	0642797	15/03/95	NONE		
WO-A1-	9211849	23/07/92	AU-A-	1252592	17/08/92
			US-A-	5128140	07/07/92
EP-A1-	0365947	02/05/90	SE-T3-	0365947	
			AU-B,B-	612525	11/07/91
			AU-A-	4365089	03/05/90
			CA-A-	2000932	26/04/90
			DE-T-	68907177	13/01/94
			ES-T-	2055775	01/09/94
			HK-A-	123394	18/11/94
			IE-B-	62640	22/02/95
			JP-A-	2164821	25/06/90
			LV-B-	10382	20/12/95
			PT-B-	92103	09/08/95
			SE-A-	8803822	26/10/88
			SG-A-	123894	17/03/95
			US-A-	5178868	12/01/93



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 47/48, 31/44	A1	(11) International Publication Number: WO 96/38175 (43) International Publication Date: 5 December 1996 (05.12.96)
(21) International Application Number: PCT/JP96/01427 (22) International Filing Date: 28 May 1996 (28.05.96) (30) Priority Data: 7/136816 2 June 1995 (02.06.95) JP (71) Applicant (for all designated States except US): TAKEDA CHEMICAL INDUSTRIES, LTD. [JP/JP]; 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP). (72) Inventors; and (75) Inventors/Applicants (for US only): ISHIGURO, Toshihiro [JP/JP]; 12-9, Kofudai 4-chome, Toyono-cho, Toyono-gun, Osaka 563-01 (JP). NAKAMICHI, Masanari [JP/JP]; 152- 20, Higashisonoda-cho 4-chome, Amagasaki-shi, Hyogo 661 (JP). OGAWA, Yasuaki [JP/JP]; 77-42, Koaza-tanita, Aza- ohyamazaki, Ohyamazaki-cho, Otokuni-gun, Kyoto 618 (JP). (74) Agents: AOYAMA, Tamotsu et al.; Aoyama & Partners, IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Osaka-shi, Osaka 540 (JP).		(81) Designated States: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IS, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: STABILIZED COMPOSITION COMPRISING AN ANTIULCERATIVE BENZIMIDAZOLE (57) Abstract A stabilized composition comprising an antiulcerative benzimidazole compound, particularly a proton pump inhibitor, and a branched cyclodextrin-carboxylic acid.		

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STABILIZED COMPOSITION COMPRISING AN ANTIULCERATIVE BENZIMIDAZOLE

5

FIELD OF THE INVENTION

The present invention relates to a stabilized composition containing an antiulcerative benzimidazole compound with enhanced water-solubility. Specifically, it relates to a stabilized composition containing an antiulcerative benzimidazole compound useful as medicaments or veterinary drugs, particularly antiulcerative agents, the stability of the composition and the water-solubility of the compound being enhanced by combining it with a branched cyclodextrin-carboxylic acid which is a cyclodextrin derivative.

15

BACKGROUND OF THE INVENTION

It is the most general and important problem in the field of pharmaceuticals to enhance the water-solubility of water-insoluble or slightly water-soluble drugs and the stability of the composition containing the drugs. Cyclodextrins have been used as effective means to solve this problem. Cyclodextrins have been used for providing suitable volatility or improving taste or smell, or for emulsification,

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powdering or stabilization, as well as for enhancing solubility of medicaments, etc. It is believed that these effects of cyclodextrins are produced by the formation of complexes containing active ingredients of pharmaceutical compositions, etc., in the cyclodextrins.

Various homologs of such cyclodextrins are known. Their water solubilities vary with their kinds. For example, α -, β - and γ -cyclodextrins consist of six, seven and eight glucose units, respectively, that are joined in such a way as to form a ring, and it is reported that the water-solubilities of α -, β - and γ -cyclodextrins are about 15%, about 2% and about 23%, respectively.

SUMMARY OF THE INVENTION

The present inventors have intensively studied how to enhance the water-solubility of antiulcerative benzimidazole compounds and the stability of the compositions containing the compounds. As a result, it has been found that use of a cyclodextrin having certain improved characteristics can achieve the above objects. Thus, the present invention has been completed.

The present invention provides a stabilized composition comprising an antiulcerative benzimidazole compound and a branched cyclodextrin-carboxylic acid or a salt thereof.

- 3 -

The present invention also provides a method of enhancing stability of a composition containing an antiulcerative benzimidazole compound, which comprises combining an antiulcerative benzimidazole compound with a
5 branched cyclodextrin-carboxylic acid or a salt thereof.

The present invention also provides a method of enhancing solubility in water of an antiulcerative benzimidazole compound, which comprises combining the antiulcerative benzimidazole compound with a branched
10 cyclodextrin-carboxylic acid or a salt thereof.

In the present invention, the antiulcerative benzimidazole compound is preferably a proton pump inhibitor, in particular lansoprazole or omeprazole. Preferably, the composition further comprises a pH adjusting agent, preferably
15 meglumine. The composition is preferably an injectable composition, and is preferably miscible with a transfusion solution.

The composition of the present invention is particularly stable in a solid form, in particular a
20 lyophilized form.

DETAILED DESCRIPTION OF THE INVENTION

The branched cyclodextrin-carboxylic acid to be used in the present invention is intended to include its free carboxylic acid, and a salt thereof with an alkali metal

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(e.g., lithium, sodium, potassium, etc.), alkaline earth metal (e.g., calcium, magnesium, etc.), etc. These branched cyclodextrin-carboxylic acids can be used alone or in combination thereof, or as mixtures of their free carboxylic acids and salts thereof.

The branched cyclodextrin-carboxylic acid is a cyclodextrin having an organic group containing at least one carboxyl group at the 6-O-position of at least one glucose unit of the cyclodextrin ring.

The cyclodextrin ring in the branched cyclodextrin-carboxylic acid has, for example, 6, 7 or 8 glucose units. Preferably, the cyclodextrin ring has 7 glucose units. Examples of the cyclodextrin include α -cyclodextrin, β -cyclodextrin and γ -cyclodextrin.

It is preferred that the organic group containing at least one carboxyl group has 1 to 3 glucose units, and that at least one of the hydroxymethyl groups of the glucose units in the organic group is oxidized to a carboxyl group.

Examples of the branched cyclodextrin-carboxylic acid include 6-O-cyclomaltohexaosyl-(6-1)- α -D-glucosyl-(4-1)-O- α -D-glucuronic acid (cyclomaltohexaosyl-(6-1)-O- α -D-glucopyranosyl-(4-1)-O- α -D-glucopyranosiduronic acid) (hereinafter also abbreviated as α -CyD-G₂-COOH; the abbreviations of the following compounds are likewise shown in the parentheses), 6-O-cyclomaltoheptaosyl-(6-1)- α -D-

- 5 -

glucosyl-(4-1)-O- α -D-glucuronic acid (cyclomaltoheptaosyl-
 (6-1)-O- α -D-glucopyranosyl-(4-1)-O- α -D-glucopyranosiduronic
 acid)(β -CyD-G₂-COOH), 6-O-cyclomaltooctaosyl-(6-1)- α -D-
 glucosyl-(4-1)-O- α -D-glucuronic acid (cyclomaltooctaosyl-
 5 (6-1)-O- α -D-glucopyranosyl-(4-1)-O- α -D-glucopyranosiduronic
 acid)(γ -CyD-G₂-COOH), 6-O-cyclomaltohexaosyl-(6-1)- α -D-
 glucuronic acid (cyclomaltohexaosyl-(6-1)-O- α -D-
 glucopyranosiduronic acid)(α -CyD-G₁-COOH), 6-O-
 cyclomaltoheptaosyl-(6-1)- α -D-glucuronic acid
 10 (cyclomaltoheptaosyl-(6-1)-O- α -D-glucopyranosiduronic acid)(β -
 CyD-G₁-COOH), 6-O-cyclomaltooctaosyl-(6-1)- α -D-glucuronic acid
 (cyclomaltooctaosyl-(6-1)-O- α -D-glucopyranosiduronic acid)(γ -
 CyD-G₁-COOH), 2-O-(6-cyclomaltohexaosyl)-acetic acid (α -CyD-
 CH₂COOH), 2-O-(6-cyclomaltoheptaosyl)-acetic acid (β -CyD-
 15 CH₂COOH), 2-O-(6-cyclomaltooctaosyl)-acetic acid (γ -CyD-
 CH₂COOH), 3-O-(6-cyclomaltoheptaosyl)-propionic acid (β -CyD-
 CH₂CH₂COOH), 2-hydroxy-3-O-(6-cyclomaltoheptaosyl)-propionic
 acid (3-O-(6-cyclomaltoheptaosyl)-2-hydroxy-propionic acid)(β -
 CyD-CH₂CH(OH)-COOH), 7^A, 7^C-di-O-[α -D-glucuronyl-(1-4)-O- α -D-
 20 glucosyl]-(1-6)-maltoheptaose (β -CyD-(G₂COOH)₂), 6-O-
 cyclomaltoheptaosyl-O- α -D-maltosyl-(4-1)-O- α -D-glucuronic acid
 (cyclomaltoheptaosyl-(6-1)-O- α -D-glucopyranosyl-(4-1)-O- α -D-
 glucopyranosyl-(4-1)-O- α -D-glucopyranosiduronic acid)(β -CyD-
 G₃-COOH), and their salts described above (e.g., sodium salt

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of β -CyD-G₂-COOH (sodium cyclomaltoheptaosyl-(6-1)-O- α -D-glucopyranosyl-(4-1)-O- α -D-glucopyranosiduronate (likewise abbreviated as β -CyD-G₂-COONa)).

Specifically, 6-O-cyclomaltohexaosyl-(6-1)- α -D-glucosyl-(4-1)-O- α -D-glucuronic acid (α -CyD-G₂-COOH), 6-O-cyclomaltoheptaosyl-(6-1)- α -D-glucosyl-(4-1)-O- α -D-glucuronic acid...(β -CyD-G₂-COOH) and 6-O-cyclomaltooctaosyl-(6-1)- α -D-glucosyl-(4-1)-O- α -D-glucuronic acid (γ -CyD-G₂-COOH) are branched cyclodextrin-carboxylic acids containing α -cyclodextrin (containing 6 glucose units), β -cyclodextrin (containing 7 glucose units) and γ -cyclodextrin (containing 8 glucose units), respectively. In each of these branched cyclodextrin-carboxylic acid, maltose is attached to one of the glucose units of the cyclodextrin ring through an α -(1-6) linkage, and the hydroxymethyl group (-CH₂OH) at the 6-position of the terminal glucose unit of the maltose is oxidized to a carboxyl group to give glucuronic acid.

Each of 6-O-cyclomaltohexaosyl-(6-1)- α -D-glucuronic acid (α -CyD-G₁-COOH), 6-O-cyclomaltoheptaosyl-(6-1)- α -D-glucuronic acid (β -CyD-G₁-COOH) and 6-O-cyclomaltooctaosyl-(6-1)- α -D-glucuronic acid (γ -CyD-G₁-COOH) is a branched cyclodextrin-carboxylic acid in which glucose is attached to one of the glucose units of the cyclodextrin ring through an α -(1-6) linkage, and the hydroxymethyl group (-CH₂OH) at the

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6-position of the branched glucose is oxidized to a carboxyl group to give glucuronic acid.

Further, 2-O-(6-cyclomaltohexaosyl)-acetic acid (α -CyD-CH₂COOH), 2-O-(6-cyclomaltoheptaosyl)-acetic acid (β -CyD-CH₂COOH) and 2-O-(6-cyclomaltooctaosyl)-acetic acid (γ -CyD-CH₂COOH) are preferable branched cyclodextrin-carboxylic acid wherein a carboxymethyl group is attached as a branch to one of the glucose units of the cyclodextrin ring.

These branched cyclodextrin-carboxylic acids or salts thereof are described in EP-A 0599646 (JP-A 7-076594) and in EP-A 0657176, and can be prepared, for example, by the methods described in the literatures.

In the present invention, the water-solubility of an antiulcerative benzimidazole compound and the stability of the compositions containing the compound can be enhanced by formulating the compound together with a branched cyclodextrin-carboxylic acid.

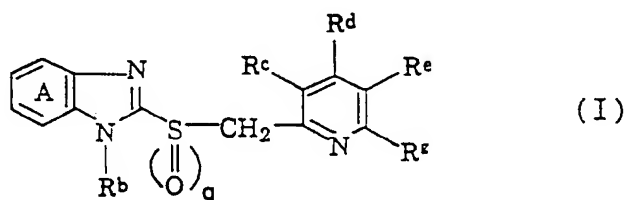
The antiulcerative benzimidazole compound to be used is normally a proton pump inhibitor having a water-solubility of not more than 10 mg/ml.

The term proton pump inhibitor as used herein is defined as a drug that suppresses acid secretion by directly or indirectly inhibiting H/K-ATPase, which functions as a proton pump in gastric mucosal acid secreting cells (parietal cells). Representative examples of such drugs include

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omeprazole, lansoprazole, pantoprazole, pariprazole sodium, leminoprazole, TY-11345, TU-199, FPL-65372, BY-686, Tannic acid, Ellagic acid, Ebselen, AHR-9294, Cassigarol-A, Bafilomycin, Y-25942, Xanthoangelol E, SK&F-96356, (-)-
 5 Epigallocatechin gallate, WY-27198, T-330 and KF-20054.

In detail, proton pump inhibitors include benzimidazole compounds, which possess proton pump inhibitory activities and are of low toxicity. Preferable benzimidazole compounds include 2-[(pyridyl)-methylsulfinyl or -
 10 methylthio]benzimidazole derivatives and salt thereof. A compound (or salt thereof) represented by formula (I) below is more preferred.



wherein ring A may optionally be substituted; R^b is a hydrogen atom, an alkyl group, an acyl group, a carboalkoxy group, a
 15 carbamoyl group, an alkylcarbamoyl group, a dialkylcarbamoyl group or an alkylsulfonyl group; R^c , R^e , and R^f are, the same or different, a hydrogen atom, an alkyl group, an alkoxy group or an alkoxyalkoxy group; R^d is a hydrogen atom, an alkyl group or a group represented by $-OR^f$ in which R^f represents a

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hydrocarbon group which may optionally be substituted; q is 0 or 1.

Benzimidazole compounds above are described in USP 4,045,563, USP 4,255,431, USP 4,359,465, USP 4,472,409, USP 4,508,905, USP 5,039,806 (JP-A 59181277), USP 4,628,098, USP 4,738,975, USP 5,045,321, USP 4,786,505, USP 4,853,230, USP 5,045,552, EP-A-295603, USP 5,312,824, EP-A-166287, EP-A-519365, and other publications.

With respect to formula (I) above, the substituent that may optionally be present on ring A includes halogen atoms, alkyl groups which may be substituted for, cycloalkyl groups which may be substituted for, alkenyl groups which may be substituted for, alkoxy groups which may be substituted for, cyano groups, carboxy groups, carboalkoxy groups, carboalkoxyalkyl groups, carbamoyl groups, carbamoylalkyl groups, hydroxy groups, hydroxyalkyl groups, acyl groups, carbamoyloxy groups, nitro groups, acyloxy groups, aryl groups, aryloxy groups, alkylthio groups and alkylsulfinyl groups, and the like.

The above substituents are hereinafter described.

Halogen atoms include fluorine, chlorine, bromine and iodine. Fluorine and chlorine are preferred, with greater preference given to fluorine.

The alkyl group in the alkyl group which may be substituted is exemplified by straight-chain or branched alkyl

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groups having 1 to 10 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl). Straight-chain or branched alkyl groups having 1 to 5 6 carbon atoms are preferred, with greater preference given to straight-chain or branched alkyl groups having 1 to 3 carbon atoms. Substituents on the substituted alkyl group include halogens, nitro, cyano groups, hydroxy groups, carboxy groups, amidino groups, guanidino groups, carbamoyl groups, 10 amino groups which may have 1 to 2 alkyl groups, acyl groups or other substituents, and the like.

The cycloalkyl group in the cycloalkyl group which may be substituted is exemplified by cycloalkyl groups having 3 to 7 carbon atoms, such as cyclopropyl, cyclobutyl, 15 cyclopentyl, cyclohexyl and cycloheptyl, etc. The cycloalkyl group may be substituted by, for example, halogens, nitro, cyano groups, hydroxy groups, carboxy groups, amidino groups, guanidino groups, carbamoyl groups, amino groups which may have 1 to 2 alkyl groups, acyl groups or other substituents, 20 and the like.

The alkenyl group in the alkenyl group which may be substituted is exemplified by straight-chain or branched alkenyl groups having 2 to 16 carbon atoms. Such alkenyl groups include allyl, vinyl, crotyl, 2-penten-1-yl, 3-penten- 25 1-yl, 2-hexen-1-yl, 3-hexen-1-yl, 2-methyl-2-propen-1-yl and

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3-methyl-2-buten-1-yl. Straight-chain or branched alkenyl groups having 2 to 6 carbon atoms are preferred, with greater preference given to straight-chain or branched alkenyl groups having 2 to 4 carbon atoms. The alkenyl group may be substituted by, for example, halogens, nitro, cyano groups, amidino groups, guanidino groups amino groups which may have 1 to 2 alkyl groups, acyl groups or other substituents, and the like. The alkenyl group mentioned above includes isomers (E- and Z-configurations) with respect to double bond.

10 The alkoxy group in the alkoxy group which may be substituted is exemplified by alkoxy groups having 1 to 10 carbon atoms. Such alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentoxy, isopentoxy, neopentoxy, hexyloxy, 15 heptyloxy, octyloxy, nonyloxy, cyclobutoxy, cyclopentoxy and cyclohexyloxy. Alkoxy groups having 1 to 6 carbon atoms are preferred, with greater preference given to alkoxy groups having 1 to 3 carbon atoms. The alkoxy group may be substituted by, for example, halogens, nitro, amidino groups, 20 guanidino groups amino groups which may have 1 to 2 alkyl groups, acyl groups or other substituents, and the like

 The halogen as a substituent on the above-described alkyl, cycloalkyl, alkenyl or alkoxy group is exemplified by chlorine, bromine, fluorine and iodine.

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The alkyl group in the alkylamino group as a substituent on the above-described alkyl, cycloalkyl, alkenyl or alkoxy group is preferably exemplified by straight-chain or branched alkyl groups having 1 to 6 carbon atoms. Such
5 alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, isopentyl, n-hexyl and isohexyl. Among other, straight-chain or branched alkyl groups having 1 to 4 carbon atoms are preferred.

The acyl group in the acylamino group as a
10 substituent on the above-described alkyl, cycloalkyl, alkenyl or alkoxy group is exemplified by acyl groups derived from organic carboxylic acids, with preference given to alkanoyl groups having 1 to 6 carbon atoms. Such alkanoyl groups include formyl, acetyl, propionyl, butyryl, isobutyryl,
15 valeryl, isovaleryl, pivaloyl and hexanoyl, with greater preference given to alkanoyl groups having 1 to 4 carbon atoms.

The number of substituents on the above-described alkyl, cycloalkyl, alkenyl or alkoxy group is 1 to 6,
20 preferably 1 to 3.

The substituted alkyl groups include trifluoromethyl, trifluoroethyl, difluoromethyl, trichloromethyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, methoxyethyl, ethoxyethyl, 1-methoxyethyl, 2-methoxyethyl, 2,2-dimethoxyethyl, 2,2-diethoxyethyl and 2-diethylphosphorylethyl, among
25

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others. Difluoromethyl, trifluoromethyl and hydroxymethyl are preferred, with greater preference given to trifluoromethyl.

The substituted cycloalkyl groups include 2-aminocyclopropan-1-yl, 4-hydroxycyclopentan-1-yl and 2,2-difluorocyclopentan-1-yl, among others.

The substituted alkenyl groups include 2,2-dichlorovinyl, 3-hydroxy-2-propen-1-yl and 2-methoxyvinyl, among others.

The substituted alkoxy groups include difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, 2-methoxyethoxy, 4-chlorobenzyloxy and 2-(3,4-dimethoxyphenyl)-ethoxy, among others. Difluoromethoxy is preferred.

The alkoxy group in the carboalkoxy group is exemplified by alkoxy groups having 1 to 7 carbon atoms (e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentoxy, isopentoxy, neopentoxy, hexyloxy, heptyloxy).

The alkoxy group in the carboalkoxyalkyl group is exemplified by alkoxy groups having 1 to 4 carbon atoms (e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy). The alkyl group in the carboalkoxyalkyl group is exemplified by alkyl groups having 1 to 4 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl). Such carboalkoxyalkyl groups include carbomethoxymethyl, 2-

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carbomethoxyethyl, 2-carbomethoxypropyl, carboethoxymethyl, 2-carboethoxyethyl, 1-carbomethoxypropyl, carbopropoxymethyl and carbobutoxymethyl.

5 The alkyl group in the carbamoylalkyl group is exemplified by alkyl groups having 1 to 4 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl).

10 The alkyl group in the hydroxyalkyl group is exemplified by alkyl groups having 1 to 7 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl, heptyl).

15 The acyl group as such or the acyl group in the acyloxy group is exemplified by alkanoyl groups having 1 to 4 carbon atoms such as formyl, acetyl, propionyl, butyryl and isobutyryl.

The aryl group as such or the aryl group in the aryloxy group is exemplified by aryl groups having 6 to 12 carbon atoms (e.g., phenyl, naphthyl).

20 The alkyl in the alkylthio group or alkylsulfinyl group is exemplified by alkyl groups having 1 to 6 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl).

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The number of substituents on substituted ring A is preferably 1 to 4, more preferably 1 to 2. Such substituents on the benzene ring may be present at 4- and 5-positions, with preference given to 5-position.

5 Ring A is preferably a ring which may optionally be substituted by i) a halogen atom, ii) an alkyl group which may be substituted, iii) a cycloalkyl group which may be substituted, iv) an alkenyl group which may be substituted, or v) an alkoxy group which may be substituted.

10 The alkyl group for R^b is exemplified by alkyl groups having 1 to 5 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl). The acyl group for R^b is exemplified by acyl groups having 1 to 4 carbon atoms, such as alkanoyl groups having 1 to 4 carbon atoms. The alkoxy in
15 the carboalkoxy group is exemplified by alkoxy groups having 1 to 4 carbon atoms (e.g., formyl, acetyl, propionyl, butyryl, isobutyryl). The alkyl in the alkylcarbamoyl group and dialkylcarbamoyl group is exemplified by alkyl groups having
20 1 to 4 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl). The alkyl in the alkylsulfonyl group is exemplified by the above-mentioned alkyl groups having 1 to 4 carbon atoms. R^b is preferably hydrogen.

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The alkyl group for R^c , R^e or R^g is exemplified by straight-chain or branched alkyl groups having 1 to 10 carbon atoms (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl). Straight-chain or branched alkyl groups having 1 to 6 carbon atoms are preferred, with greater preference given to straight-chain or branched alkyl groups having 1 to 3 carbon atoms.

The alkoxy group for R^c , R^e or R^g is exemplified by alkoxy groups having 1 to 10 carbon atoms (e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentoxy, isopentoxy, neopentoxy, hexyloxy, heptyloxy, octyloxy, nonyloxy). Alkoxy groups having 1 to 6 carbon atoms are preferred, with greater preference given to alkoxy groups having 1 to 3 carbon atoms.

The alkoxy in the alkoxyalkoxy group for R^c , R^e or R^g is exemplified by alkoxy groups having 1 to 4 carbon atoms (e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy).

R^c is preferably a hydrogen atom, an alkyl group or an alkoxy group. R^e is preferably a hydrogen atom, an alkyl group or an alkoxy group. R^g is preferably a hydrogen atom.

The alkyl group for R^d is exemplified by alkyl groups having 1 to 4 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl).

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The hydrocarbon group in the hydrocarbon group which may optionally be substituted, for R^f , is exemplified by hydrocarbon groups having 1 to 13 carbon atoms, such as straight-chain or branched alkyl groups having 1 to 6 carbon atoms (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, pentyl, isopentyl, hexyl), alkenyl groups having 2 to 6 carbon atoms (e.g., vinyl, allyl, 2-butenyl, methylallyl, 3-butenyl, 2-pentenyl, 4-pentenyl, 5-hexenyl), alkynyl groups having 2 to 6 carbon atoms (e.g., ethynyl, propargyl, 2-butyne-1-yl, 3-butyne-2-yl, 1-pentyne-3-yl, 3-pentyne-1-yl, 4-pentyne-2-yl, 3-hexyne-1-yl), cycloalkyl groups having 3 to 6 carbon atoms (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), cycloalkenyl groups having 3 to 6 carbon atoms (e.g., cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl), aralkyl groups having 7 to 13 carbon atoms (e.g., benzyl, 1-phenethyl, 2-phenethyl) and aryl groups having 6 to 10 carbon atoms (e.g., phenyl, naphthyl). Straight-chain or branched alkyl groups having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, pentyl, isopentyl, hexyl) are preferred, with greater preference given to straight-chain or branched alkyl groups having 1 to 4 carbon atoms.

The substituent group in the substituted hydrocarbon group is exemplified by C_{6-10} aryl groups (e.g., phenyl, naphthyl), amino, C_{1-6} alkylamino groups (e.g., methylamino,

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ethylamino, isopropylamino), di-C₁₋₆ alkylamino groups (e.g., dimethylamino, diethylamino), N-aralkyl-N-cycloalkylamino groups (e.g., N-benzyl-N-cyclohexylamino), N-aralkyl-N-alkylamino groups (e.g., N-(1-naphthylmethyl)-N-ethylamino),
5 azide, nitro, halogens (e.g., fluorine, chlorine, bromine, iodine), hydroxyl, C₁₋₄ alkoxy groups (e.g., methoxy, ethoxy, propoxy, butoxy), C₆₋₁₀ aryloxy groups (e.g., phenoxy, naphthyloxy), C₁₋₆ alkylthio groups (e.g., methylthio, ethylthio, propylthio), C₆₋₁₀ arylthio groups (e.g., phenylthio, naphthylthio), cyano, carbamoyl groups, carboxyl groups, C₁₋₄ alkoxycarbonyl groups (e.g., methoxycarbonyl, ethoxycarbonyl), C₇₋₁₁ aryloxycarbonyl groups (e.g., phenoxy-
10 carbonyl, 1-naphthyloxycarbonyl, 2-naphthyloxy-carbonyl), carboxy-C₁₋₄ alkoxy groups (e.g., carboxymethoxy, 2-carboxyethoxy), C₁₋₆ alkanoyl groups (e.g., formyl, acetyl, propionyl, isopropionyl, butyryl, pentanoyl, hexanoyl), C₇₋₁₁ alloyl groups (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl), C₆₋₁₀ arylsulfonyl groups (e.g., benzenesulfonyl, 1-naphthylsulfonyl, 2-naphthylsulfonyl), C₁₋₆ alkylsulfinyl groups (e.g.,
15 methylsulfinyl, ethylsulfinyl), C₆₋₁₀ arylsulfinyl groups (e.g., benzenesulfinyl, 1-naphthylsulfinyl, 2-naphthylsulfinyl), C₁₋₆ alkylsulfonyl groups (e.g., methylsulfonyl, ethylsulfonyl), 5- or 6-membered heterocyclic groups (e.g., 2-furyl, 2-thienyl, 4-thiazolyl, 4-imidazolyl, 4-pyridyl, 1,3,4-

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thiadiazol-2-yl, 1-methyl-5-tetrazolyl) containing 1 to 4 heteroatoms (e.g., nitrogen, oxygen, sulfur), 5- or 6-membered heterocyclic carbonyl groups (e.g. 2-furoyl, 2-thienoyl, nicotinoyl, isonicotinoyl) containing 1 to 4 heteroatoms (e.g., nitrogen, oxygen, sulfur), 5- or 6-membered heterocyclic thio groups (e.g., 4-pyridylthio, 2-pyrimidylthio, 1,3,4-thiadiazol-2-ylthio, 1-methyl-5-tetrazolylthio) containing 1 to 4 heteroatoms (e.g., nitrogen, oxygen, sulfur). The heterocyclic thio group may condense with the benzene ring to form a bicyclic condensed thio group (e.g., 2-benzothiazolylthio, 8-quinolylthio). Halogens (e.g., fluorine, chlorine, bromine, iodine), hydroxyl and C₁₋₄ alkoxy groups (e.g., methoxy, ethoxy, propoxy, butoxy) are preferred.

The number of substituents is normally 1 to 5, preferably 1 to 3.

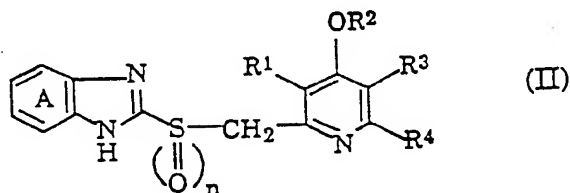
R^d is preferably an alkoxy group which may be substituted, or an alkoxyalkoxy group which may be substituted. The alkoxy in the alkoxy group which may be substituted is exemplified by alkoxy groups having 1 to 8 carbon atoms (e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentoxy, isopentoxy, neopentoxy, hexyloxy, heptyloxy, octyloxy). The alkoxy in the alkoxyalkoxy group which may be substituted is exemplified by alkoxy groups having 1 to 4 carbon atoms (e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy,

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sec-butoxy, tert-butoxy). R^d is more preferably an alkoxy group having 1 to 8, preferably 1 to 4 carbon atoms, which may be halogenated, or an alkoxyalkoxy group which may be halogenated. Preferred alkoxy groups which may be halogenated include 2,2,2-trifluoroethoxy, 2,2,3,3,3-pentafluoropropoxy, 1-(trifluoromethyl)-2,2,2-trifluoroethoxy, 2,2,3,3-tetrafluoropropoxy, 2,2,3,3,4,4,4-heptafluorobutoxy, 2,2,3,3,4,4,5,5-octafluoropentoxy and methoxy. Preferred alkoxyalkoxy groups which may be halogenated include 3-methoxypropoxy.

q is preferably 0.

More specifically, the benzimidazole compound for the present invention is exemplified by a compound represented by formula (II):



wherein ring A may optionally be substituted; R^1 , R^3 and R^4 are, the same or different, hydrogen, or an alkyl or alkoxy group; R^2 is a hydrocarbon group which may optionally be substituted; n is 0 or 1.

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With respect to formula (II) above, ring A is exemplified by the same rings as those mentioned for ring A of formula (I) above.

5 The alkyl group for R^1 , R^3 or R^4 is exemplified by straight-chain or branched alkyl groups having 1 to 10 carbon atoms. Such alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl and decyl. Straight-chain or branched alkyl groups having 1 to 6 carbon
10 atoms are preferred, with greater preference given to straight-chain or branched alkyl groups having 1 to 3 carbon atoms.

The alkoxy group for R^1 , R^3 or R^4 is exemplified by alkoxy groups having 1 to 10 carbon atoms. Such alkoxy groups
15 include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentoxy, isopentoxy, neopentoxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, cyclobutoxy, cyclopentoxy and cyclohexyloxy. Alkoxy groups having 1 to 6 carbon atoms are preferred, with greater
20 preference given to alkoxy groups having 1 to 3 carbon atoms.

The hydrocarbon group which may optionally be substituted, for R^2 , is exemplified by the same hydrocarbon groups as those mentioned for R^f above.

R^1 is preferably C_{1-6} alkyl or C_{1-6} alkoxy, more
25 preferably C_{1-3} .

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R^3 is preferably hydrogen or C_{1-6} alkyl, more preferably hydrogen.

R^2 is preferably C_{1-4} alkoxy which may optionally be substituted by i) halogen, ii) hydroxyl or iii) C_{1-4} alkoxy, more preferably, C_{1-3} alkyl which may optionally be substituted by i) halogen or ii) C_{1-4} alkoxy.

R^4 is preferably hydrogen.

Examples of benzimidazole compounds for the present invention include 2-[2-[3-methyl-4-(2,2,3,3-tetrafluoropropoxy)pyridyl]methylthio]benzimidazole, 2-[2-[3-methyl-4-(2,2,2-trifluoroethoxy)pyridyl]methylsulfinyl]benzimidazole (lansoprazole), 2-[(2-pyridyl)methylsulfinyl]benzimidazole (timoprazole), 2-[2-(3,5-dimethyl-4-methoxypyridyl)methylsulfinyl]-5-methoxy-1H-benzimidazole (omeprazole), sodium salt of 2-[2-[4-(3-methoxypropoxy)-3-methyl]pyridyl]methylsulfinyl-1H-benzimidazole and 2-[2-(3,4-dimethoxy)pyridyl]methylsulfinyl-5-difluoromethoxy-1H-benzimidazole (pantoprazole).

Among others, lansoprazole and omeprazole are preferably applied to the present invention.

A benzimidazole compound (or salt thereof) for the present invention is produced by, for example, the above-described known methods described in Japanese or European Patent Publications and U.S. Patents, or modifications thereof.

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The salt of a benzimidazole compound is preferably used as a physiologically acceptable salt. Physiologically acceptable salts include salts with inorganic bases, salts with organic bases and salts with basic amino acids. Useful inorganic bases include alkali metals (e.g., sodium, potassium) and alkaline earth metals (e.g., calcium, magnesium). Useful organic bases include trimethylamine, triethylamine, pyridine, picoline, N,N-dibenzylethylenediamine, ethanolamine, diethanolamine, trishydroxymethylaminomethane and dicyclohexylamine. Useful basic amino acids include arginine and lysine.

These salts are produced by known methods such as those described in EP-A-295603 and USP 4,738,974, or modifications thereof.

In the present invention, the mixing ratio of the branched cyclodextrin-carboxylic acid to the antiulcerative benzimidazole compounds is not limited and can be selected from wide ranges. However, considering the water-solubility of the compounds, the amount of the branched cyclodextrin-carboxylic acid to be used is 0.1 to 20 mol, preferably 0.1 to 10 mol, more preferably 0.2 to 5 mol, particularly preferably 2 to 5 mol, per mol of the antiulcerative benzimidazole compound.

The composition of the present invention can be prepared by mixing the branched cyclodextrin-carboxylic acid

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with the antiulcerative benzimidazole compound according to known methods. Roughly speaking, the inclusion compound of the antiulcerative benzimidazole compound included in the branched cyclodextrin-carboxylic acid can be prepared, for example, by the following four methods:

(1) Co-precipitation method (Crassons, et al., 5th Int. Conf. Pharmaceutical Technology, Paris, May 30 to June 1, 1989),

(2) Lyophilizing or spray drying method (Kurozumi et al., Chem. Pharm. Bull., 23, 3062 (1975); Kata et al., Pharmazie 39, 856 (1984)),

(3) Phase - solubility curve crystallization method (Uekama et al., Int. J. Pharm. 10,1 (1982)),

(4) Milling method (J. Szejtli et al., "Cyclodextrins and their inclusion complexes", Akademiai Kiado, Budapest (1982), p. 109-114; Kyowa Jap. Prov. Pat. Pubin. No. 106 698 (1982)).

Specifically, the inclusion compound can be prepared as follows:

(1) A compound to be included in the inclusion compound is added to an aqueous solution of the branched cyclodextrin-carboxylic acid (hereinafter sometimes referred to as the cyclodextrin). The mixture is stirred (shaken), if necessary, under warming. The remaining unreacted compound

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to be included is removed by filtration, centrifugation, etc., to obtain an inclusion compound.

(2) The cyclodextrin is dissolved in water, and a compound to be included is added thereto. The two are mixed for 10 minutes to several hours, followed by lyophilization (M. Kurozumi et al., Chem. Pharm. Bull., 23, 142 (1975)) to give powder. This powder is dissolved in water, and the unreacted compound to be included is removed to obtain an aqueous solution of an inclusion compound.

(3) A compound to be included is dissolved in an appropriate water-soluble organic solvent in advance. This solution is contacted with cyclodextrin in an aqueous solution. Then the organic solvent and water are evaporated in vacuo or lyophilized (EP-A-519428, JP-A 5 (1992)-178765), and water is then added to the residue to dissolve it, and the unreacted compound to be included is removed to obtain an aqueous solution of an inclusion compound.

(4) When an acidic compound is included in the inclusion compound, it is dissolved in ammonia water and cyclodextrin is added thereto, and the mixture is lyophilized. During the lyophilization, excess ammonia is removed and an inclusion compound is obtained as an ammonium salt of the acidic compound.

(5) A compound to be included is dissolved in a lipophilic organic solvent (e.g., ethyl ether, etc.), and the

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solution is mixed with a saturated aqueous solution of the cyclodextrin. The mixture is shaken vigorously for 10 minutes to several hours and then allowed to stand in a cold place overnight to precipitate an inclusion compound. The precipitate is separated by centrifugation or filtration. The resulting powder is dissolved in water to give an aqueous solution of an inclusion compound.

(6) A powdered compound to be included and powdered cyclodextrin are mixed, and a small amount of water is added thereto. The mixture is kneaded (Y. Nakai et al., Chem. Pharm. Bull., 26, 2419 (1978)) and then, if necessary, lyophilized.

(7) An aqueous solution of the cyclodextrin and an aqueous solution of a compound to be included are mixed to give an aqueous solution of an inclusion compound.

In particular, the above method (3) is useful for solubilization of antiulcerative benzimidazole compounds.

In many cases, the aqueous solution or powder thus obtained by the known methods giving inclusion compounds contains an inclusion compound or a complex formed by electrostatic or hydrophobic interactions or hydrogen bonds, etc. Therefore, the term "inclusion compound" used in the present invention means not only an inclusion compound or a complex per se but also a mixture of an inclusion compound, a complex, a free compound to be included and/or a free

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cyclodextrin. That is, the powder and aqueous solution obtained may contain, other than an inclusion compound or a complex, a water-insoluble or slightly water-soluble compound that is not included or complexed, and/or free cyclodextrin.

5 The inclusion compound per se and powder and an aqueous solution like this have extremely high water-solubilities and dissolve in water instantly.

The composition of the present invention may be the aqueous solution or powder per se thus obtained, or it may be

10 a pharmaceutical composition in an appropriate dosage form, a veterinary composition, etc., prepared using known additives such as excipients, binders or lubricants.

For example, to improve properties of the powder obtained above (packing capacity into a storage bottle or a

15 vial, specific volume, destaticizing, etc.), saccharides, antiseptics, stabilizers, antistatic agents, etc., can be added. For example, when injections are prepared, the powder obtained by this operation readily dissolves in an aqueous isotonic solution prepared using distilled water or sodium

20 chloride and saccharides (e.g., glucose, mannitol, inositol, etc.). After dissolution, the resulting injectable preparation containing an active ingredient can be administered intravenously, intramuscularly, subcutaneously, into organs, or directly to foci such as tumor or excised

25 parts of tumor, in a drug concentration effective in vivo

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against the diseases to be treated. When oral preparations are prepared, tablets, capsules, granules, fine granules, enveloped preparations, drops, liquids, etc., can be prepared. On formulating these preparations, known excipients, lubricants, binders, dispersers, stabilizers, colorants and absorption-improving (promoting) agents, etc., can normally be used.

The above powder can also be formulated into preparations other than injectable or oral preparations according to conventional methods. Examples of such preparations are preparations administered to mucous membranes such as nose, the rectum. Each of the above preparations can be molded into various controlled-release preparations or preparations for targeting therapies, and the composition of the present invention can be used as a raw material of such preparations.

In the present invention, the composition is preferably an injectable composition, especially intravenously injectable solution. In terms of the stability of the composition, the composition preferably further contains a pH adjusting agent, such as meglumine, sodium hydroxide, potassium hydroxide, ammonia water, sodium bicarbonate, sodium carbonate, triethanolamine, monoethanolamine, diisopropanolamine, triisopropanolamine and L-arginine. The amount of the pH adjusting agent to be used is 0.01 to 10 mol,

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preferably 0.1 to 5 mol, per mol of the antiulcerative benzimidazole compound. Preferably, the composition is miscible with a transfusion solution, and can be used as a mixture of the composition and a transfusion solution. Any commercially available or conventional transfusion solution can be used. Examples of the transfusion solution include glucose injection, xylitol injection, D-mannitol injection, fructose injection, isotonic sodium chloride solution, dextran 40 injection, dextran 70 injection, amino acid injection, Ringer's injection, lactated Ringer's injection. The ratio of the composition to the transfusion solution is 1/1 (v/v) to 1/500 (v/v), preferably 1/20 (v/v) to 1/100 (v/v).

As described above, the branched cyclodextrin-carboxylic acid used in the present invention enhances the water-solubility of antiulcerative benzimidazole compounds and has high safety to the living body. Therefore, the composition of the present invention is applicable to the prevention and treatment of animal ulcers, and is particularly effective in the prevention and treatment of digestive ulcers in mammals (e.g., humans, monkeys, cattle, dogs, swine, etc.). Examples of such digestive ulcers include gastric ulcer, duodenal ulcer, reflux esophagitis, anastomotic ulcer, acute and chronic gastritis. Specifically, for example, the composition comprising lansoprazole as the antiulcerative benzimidazole compound can be used in accordance with the

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manner described in EP 0174726. The composition of the present invention can be administered in an appropriate dosage form such as injections, oral preparations, syrups, preparations externally administered to skin, pernasal preparations, rectal suppositories or preparations applied to mucous membranes.

Although the dose of the composition of the present invention is chosen as appropriate, according to ulcer type, symptoms, age and the other factors, for example, in the case of the compositions of proton pump inhibitors, the compositions are administered at the dose of 0.01 mg/kg/day - 50 mg/kg/day, preferably 0.1 - 3 mg/kg/day, more preferably 0.1 - 1 mg/kg/day, as the dose of the proton pump inhibitors. Specifically, in the case of the composition of lansoprazole, the daily dose of lansoprazole is 0.01 - 30 mg/kg, more preferably 0.1 - 3 mg/kg.

The following examples further illustrate the present invention in detail, but are not to be construed to limit the scope thereof.

Example 1

Lansoprazole [(±)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole] (19 mg) was dissolved in methanol (10 ml). Separately from this solution, sodium 6-O-cyclomatoheptaosyl-(6-1)-α-D-glucosyl-(4-1)-O-α-D-glucuronate (β-CyD-G₂-COONa) (384 mg) was dissolved in water

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(10 ml). The aqueous solution was added to the methanol solution with stirring, and the mixture was stirred for 30 seconds. The solvent in the resulting solution was evaporated under reduced pressure. The residue was dissolved in water
5 (2 ml), and the solution was filtered through a membrane filter (0.22 μ m).

Separately, lansoprazole alone was added to water. The mixture was shaken at room temperature, and filtered through a membrane filter (0.22 μ m).

10 The lansoprazole in the above homogeneous aqueous solution and filtrate was determined by high performance liquid chromatography (HPLC).

HPLC conditions:

Column : YMC AQ-312, 6 μ m x 15 cm
15 Mobile phase : H₂O:CH₃CN:triethylamine = 60:40:1
(pH 7.0)
Flow rate : 1 ml/min
Temperature : Room temperature
Detection : UV 285 nm

20 The results are as follows.

Comparison of the water-solubility of the antiulcerative compound

Lansoprazole combined with β -CyD-G ₂ -COONa	0.892 mg/ml
Lansoprazole alone	0.007 mg/ml

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The results show that addition of β -CyD-G₂-COONa remarkably increased the water-solubility of the antiulcerative compound compared with the case in which the antiulcerative compound was used alone.

5

Example 2

Lansoprazole [(±)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole] (19 mg) was dissolved in methanol (5 ml). Separately from this solution, sodium 6-O-cyclomatoheptaosyl-(6-1)- α -D-glucosyl-(4-1)-O- α -
10 D-glucuronate (β -CyD-G₂-COONa) (384 mg) was dissolved in water (5 ml). The aqueous solution was added to the methanol solution with stirring, and the mixture was stirred for 30 seconds. The solvent in the resulting solution was evaporated under reduced pressure. The residue was dissolved in water
15 (10 ml), and the solution was filtered through a membrane filter (0.22 μ m) and lyophilized to obtain powder. The powder (200 mg) was completely dissolved in water (200 ml).

The lyophilized composition comprising β -CyD-G₂-COONa and lansoprazole of the present invention was an
20 inclusion compound which was stable at room temperature without decomposition of the lansoprazole.

Example 3

Lansoprazole [(±)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole] (300 mg) was
25 dissolved in ethanol (50 ml). Separately from this solution,

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sodium 6-O-cyclomatoheptaosyl-(6-1)- α -D-glucosyl-(4-1)-O- α -D-glucuronate (β -CyD-G₂-COONa) (6.05 g) and meglumine (1-deoxy-1-(methyamino)-D-glucitol) (600 mg) were dissolved in water (50 ml). The pH of the solution was adjusted to 11.5 with 1N NaOH. The ethanol solution was added to the aqueous solution with stirring, and the mixture was stirred for 60 seconds. The solvent in the resulting solution was evaporated under reduced pressure. The residue was dissolved in water (50 ml), and the solution was filtered through a membrane filter (0.22 μ m) and lyophilized to obtain powder. The lansoprazole content in the resulting powder was 3.78% (w/w), and the water content in the powder was 10.9%.

Example 4

The lyophilized powder obtained in Example 3 was filled into vials (150 mg powder per vial) and dried over phosphorus pentaoxide, and each vial was sealed under an atmosphere of nitrogen gas. A preparative stability test was carried out at 40°C for 4 weeks. The water content was 0.5% after drying over phosphorus pentaoxide, and the amount of the residual lansoprazole was not less than 95% after 4 weeks.

Example 5

The lyophilized powder obtained in Example 3 was dissolved in water for injection (150 mg powder per ml of the water for injection). The solution was mixed with isotonic sodium chloride solution (Otsuka Seishoku Chu (Otsuka

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Pharmaceutical Co., Ltd.)), glucose injection (Ohtsuka Toeki
5% (Otsuka Pharmaceutical Co., Ltd.)), Ringer's solution
containing low molecular weight dextran and lactic acid (Low
Molecular Weight Dextran L Injection (Otsuka Pharmaceutical
5 Co., Ltd.)) and an electrolyte solution for transfusion
(Solita T No. 3 (Shimizu Pharmaceutical Co., Ltd.)). The
stability of lansoprazole after the addition of transfusion
solution was tested. The composition ratio of the aqueous
lyophilized powder solution to the transfusion solution was
10 1/99 (v/v). The amount of the residual lansoprazole was not
less than 98% in the isotonic sodium chloride solution and
glucose injection until 8 hours after the addition, not less
than 97% in the Ringer's solution until 4 hours after the
addition, and not less than 93% in the electrolyte solution
15 for transfusion until 4 hours after the addition.

Example 6

The lyophilized powder obtained in Example 3 was
dissolved in water for injection (150 mg powder per ml of the
water for injection). The solution was added to each of
20 Ringer's solution containing low molecular weight dextran and
lactic acid (Low Molecular Weight Dextran L Injection (Otsuka
Pharmaceutical Co., Ltd.)) and an electrolyte solution for
transfusion (Solita T No. 3 (Shimizu Pharmaceutical Co.,
Ltd.)). The stability of lansoprazole after the addition of
25 the transfusion solution was compared with that in a

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formulation containing no cyclodextrin-carboxylic acid [the formulation being a solution of lyophilized powder of lansoprazole (30 mg) containing mannitol (60 mg) and meglumine (10 mg) in an aqueous 30% polyethylene glycol 400 solution (5 ml)]. The composition ratio of the aqueous lyophilized powder solution to the transfusion solution was 1/99 (v/v). The composition ratio of the formulation containing no cyclodextrin-carboxylic acid to the transfusion solution was 1/99 (v/v).

The amounts of the lansoprazole remaining 1 hour, 4 hours and 18 hours after the addition of the Ringer's solution containing low molecular weight dextran and lactic acid were 98.9%, 97.7% and 91.0%, respectively, in the case of the composition of Example 3, compared with 80.1%, 45.6% and 4.4%, respectively, in the case of the formulation containing no cyclodextrin-carboxylic acid.

The amounts of the lansoprazole remaining 1 hour, 4 hours and 18 hours after the addition of the electrolyte solution for transfusion were 98.2%, 93.3% and 62.3%, respectively, in the case of the composition of Example 3, compared with 60.1%, 12.8% and 0%, respectively, in the case of the formulation containing no cyclodextrin-carboxylic acid.

As described above, the composition of the present invention is very stable, and the antiulcerative benzimidazole compound combined with a branched cyclodextrin-carboxylic acid

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5 according to the present invention has a much higher water-solubility compared with that of the antiulcerative benzimidazole compound alone. In addition, the branched cyclodextrin-carboxylic acid has less effect (e.g., destruction of erythrocytes) on the living body than β -cyclodextrin, and therefore is highly safe for blood. Moreover, β -CyD-G₂-COOH is hardly decomposed with acids or enzymes, and therefore the composition of the present invention is highly safe to mammals including humans.

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CLAIMS

1. A stabilized composition comprising an antiulcerative benzimidazole compound and a branched cyclodextrin-carboxylic acid or a salt thereof.

5 2. A composition according to claim 1, wherein the antiulcerative benzimidazole compound is a proton pump inhibitor.

3. A composition according to claim 1, wherein the amount of the branched cyclodextrin-carboxylic acid is 0.1 to
10 20 mol per mol of the antiulcerative benzimidazole compound.

4. A composition according to claim 1, wherein the branched cyclodextrin-carboxylic acid is a cyclodextrin having an organic group containing at least one carboxyl group at the 6-O-position of at least one glucose unit of the cyclodextrin
15 ring.

5. A composition according to claim 4, wherein the cyclodextrin ring has 7 glucose units.

6. A composition according to claim 4, wherein the organic group has 1 to 3 glucose units and at least one of the
20 hydroxymethyl groups of the glucose unit(s) in the organic group is oxidized to a carboxyl group.

7. A composition according to claim 4, wherein the organic group is 2-carboxyethyl or 2-carboxy-2-hydroxyethyl.

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8. A composition according to claim 1, wherein the branched cyclodextrin-carboxylic acid is 6-O-cyclomaltohexaosyl-(6-1)- α -D-glucosyl-(4-1)-O- α -D-glucuronic acid, 6-O-cyclomaltoheptaosyl-(6-1)- α -D-glucosyl-(4-1)-O- α -D-glucuronic acid, 6-O-cyclomaltooctaosyl-(6-1)- α -D-glucosyl-(4-1)-O- α -D-glucuronic acid, 6-O-cyclomaltohexaosyl-(6-1)- α -D-glucuronic acid, 6-O-cyclomaltoheptaosyl-(6-1)- α -D-glucuronic acid, 6-O-cyclomaltooctaosyl-(6-1)- α -D-glucuronic acid, 2-O-(6-cyclomaltohexaosyl)-acetic acid, 2-O-(6-cyclomaltoheptaosyl)-acetic acid, 2-O-(6-cyclomaltooctaosyl)-acetic acid, 3-O-(6-cyclomaltoheptaosyl)-propionic acid, 2-hydroxy-3-O-(6-cyclomaltoheptaosyl)-propionic acid, 7^A, 7^C-di-O-[α -D-glucuronyl-(1-4)-O- α -D-glucosyl]-(1-6)-maltoheptaose, or 6-O-cyclomaltoheptaosyl-O- α -D-maltosyl-(4-1)-O- α -D-glucuronic acid.

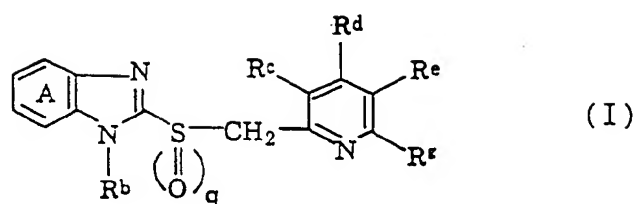
9. A composition according to claim 1, wherein the branched cyclodextrin-carboxylic acid is 6-O-cyclomaltoheptaosyl-(6-1)- α -D-glucosyl-(4-1)-O- α -D-glucuronic acid.

10. A composition according to claim 1, which is a pharmaceutical composition.

11. A composition according to claim 1, which is an antiulcerative composition.

12. A composition according to claim 1, wherein the antiulcerative benzimidazole compound is represented by the formula (I):

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wherein ring A may optionally be substituted; R^b is a hydrogen atom, an alkyl group, an acyl group, a carboalkoxy group, a carbamoyl group, an alkylcarbamoyl group, a dialkylcarbamoyl group or an alkylsulfonyl group; R^c , R^e , and R^f are, the same or different, a hydrogen atom, an alkyl group, an alkoxy group or an alkoxyalkoxy group; R^d is a hydrogen atom, an alkyl group or a group represented by $-OR^f$ in which R^f represents a hydrocarbon group which may optionally be substituted; q is 0 or 1.

10 13. A composition according to claim 1, wherein the antiulcerative benzimidazole compound is lansoprazole or omeprazole.

 14. A composition according to claim 1, which further comprises a pH adjusting agent.

15 15. A composition according to claim 14, wherein the amount of the pH adjusting agent is 0.01 to 10 mol per mol of the antiulcerative benzimidazole compound.

 16. A composition according to claim 1, wherein the pH adjusting agent is meglumine.

20 17. A composition according to claim 1, which is for injection.

INTERNATIONAL SEARCH REPORT

International Application No

PC1/JP 96/01427

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K47/48 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	EP,A,0 657 176 (TAKEDA CHEM. INDUST.) 14 June 1995 cited in the application	1
Y	see page 3, line 19 - line 55; claims 1,9 see page 6, line 14 - line 25 ---	1-23
Y	WO,A,86 00913 (BYK GULDEN LOMBERG CHEM FAB) 13 February 1986 see claim 1 ---	1-23
X	WO,A,95 07263 (SCHERING AG ; KUHNKE JOACHIM (DE); ECKLE EMIL (DE); THIERAUCH KARL) 16 March 1995 see claims ---	1,12
X,Y	DE,A,34 27 786 (BYK GULDEN LOMBERG CHEM FAB) 30 January 1986 see claims ---	1-23
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☒ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

29 July 1996

Date of mailing of the international search report

09.08.96

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INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,93 13138 (SUNKYONG IND CO LTD) 8 July 1993 see claims	1-23
X	DE,A,34 27 785 (BYK GULDEN LOMBERG CHEM FAB) 30 January 1986 see page 5, paragraph 2; claims -----	1,12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PC1/JP 96/01427

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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WO-A-8600913	13-02-86	DE-A- 3427787 AU-B- 4636885 EP-A- 0190239	30-01-86 25-02-86 13-08-86
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WO-A-9507263	16-03-95	DE-A- 4330959	16-03-95
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DE-A-3427786	30-01-86	NONE	
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DE-A-3427785	30-01-86	NONE	
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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/28, 9/50		A1	(11) International Publication Number: WO 97/02020
			(43) International Publication Date: 23 January 1997 (23.01.97)
(21) International Application Number: PCT/EP96/02892 (22) International Filing Date: 2 July 1996 (02.07.96) (30) Priority Data: 08/498,386 5 July 1995 (05.07.95) US (71) Applicant: BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH [DE/DE]; Byk-Gulden-Strasse 2, D-78467 Konstanz (DE). (72) Inventors: DIETRICH, Rango; Im Tiergarten 16, D-78465 Konstanz (DE). SACHS, George; 17986 Boris Drive, Encino, CA 91312 (US). NEY, Hartmut; Peter-Thumb-Strasse 46, D-78464 Konstanz (DE). BENEDIKT, Gerald; Winterbergstrasse 2, D-78465 Konstanz (DE). (74) Common Representative: BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH; Byk-Gulden-Strasse 2, D-78467 Konstanz (DE).			(81) Designated States: AU, BG, BR, BY, CA, CN, CZ, EE, HU, IL, JP, KR, LT, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: ORAL PHARMACEUTICAL COMPOSITION CONTAINING ANTIMICROBIAL ACTIVES AND SUSTAINED RELEASE PANTOPRAZOLE			
(57) Abstract An oral pharmaceutical composition of pantoprazole in pellet or tablet form, wherein the pantoprazole is at least partly in slow-release form, is distinguished, on combined administration with an antimicrobially-active ingredient, by an enhanced action of rapid onset against disorders caused by Helicobacter.			

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ORAL PHARMACEUTICAL COMPOSITION CONTAINING ANTIMICROBIAL ACTIVES AND SUSTAINED
RELEASE PANTOPRAZOLE

Field of the Invention

The present invention relates to oral pharmaceutical compositions in pellet or tablet form for combined use of pantoprazole with an antimicrobially-active ingredient for the treatment of disorders caused by *Helicobacter*.

Background

Pyridin-2-ylmethanysulfinyl-1H-benzimidazoles, as disclosed, for example, in EP-A 0005129, EP-A 0166287 and EP-A 0268956 are becoming increasingly important, because of their H^+/K^+ ATPase-inhibiting action, for the therapy of diseases which originate from increased gastric acid secretion. Examples of active ingredients which are already commercially available from this group are omeprazole (INN), lansoprazole (INN) and pantoprazole (INN). These active ingredients are also called irreversible proton pump inhibitors.

Control of the microbe, *Helicobacter pylori*, which is thought to be responsible for certain gastric disorders, by combined use of an antimicrobially-active ingredient which is active against *Helicobacter pylori* and of an agent which reduces gastric acid has been regarded as the method of choice for some time.

EP-A 0519365 proposes (for the active ingredient pantoprazole) a formulation based on the principle of an alkaline core coated with a water-soluble intermediate layer and with an enteric layer, where improved stability is achieved by using polyvinylpyrrolidone and/or hydroxypropylmethylcellulose as

binder for the alkaline core.

EP-A 0342522 discloses a formulation for acid-sensitive benzimidazoles, in which an intermediate layer is located between the alkaline core and the enteric coating and is composed of a film-forming material which has only low solubility in water, such as ethylcellulose and polyvinyl acetate, and of a fine-particle inorganic or organic material which is suspended therein and has low solubility in water, such as magnesium oxide, silicon oxide or sucrose fatty acid esters.

JP-A 59020219 discloses an enteric composition for acid-labile active ingredients which comprises (under the enteric coating) an intermediate layer of a film-forming material, such as hydroxypropylmethylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose phthalate with a content of higher fatty acids.

DE-A 3233764 proposes for enteric compositions an intermediate layer which is formed from a water-soluble cellulose ether and a water-soluble mono- or polybasic organic acid, such as citric acid, tartaric acid, and the like.

Combined use of irreversible proton pump inhibitors with antimicrobially-active ingredients does indeed show a good effect against *Helicobacter* in vitro. However, the clinical effect achieved with this combined use is disappointing. Of practical inconvenience is the great delay in the onset of action.

Summary of the Invention

The action of an antimicrobially-active ingredient on *Helicobacter* surprisingly is enhanced by administering pantoprazole in slow-release dosage form (extended release form). It must be regarded as particularly surprising that, in addition, administration of the slow-release pantoprazole results in the onset of action taking place significantly faster than on administration in a form without retarding such release. The duration of treatment until *Helicobacter* is eradicated is shortened, saving considerable amounts of antibiotic and acid inhibitor.

The invention thus relates to an oral pharmaceutical composition for treating a disorder caused by *Helicobacter* comprising pantoprazole in combination with at least one antimicrobially-active ingredient, wherein at least part of the pantoprazole is in slow-release form. Further subject-matters are evident from the claims.

Details

In connection with the present invention, pantoprazole is the compound, 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulfinyl]-1H-benzimidazole, its salts and solvates (e.g. hydrates), in particular the sodium salt with one and a half molecules of water of crystallization (pantoprazole Na x 1.5 H₂O).

Examples of suitable antimicrobially-active ingredients (active against *Helicobacter* and, in particular, against *Helicobacter pylori*) are enumerated in European Patent Application EP-A 0282131. These active ingredients include, for example, bismuth salts (such as bismuth subcitrate or bismuth subsalicylate), sulfonamides, nitrofurans (such as nitrofurazone, nitrofurantoin or furazolidone), metronidazole, tinidazole, nimorazole or antibiotics. Examples of antibiotics which may be mentioned in this connection are, arranged according to particular classes of active ingredient: aminoglycosides, such as gentamicin, neomycin, kanamycin, amikacin or streptomycin; macrolides, such as erythromycin, azithromycin, clarithromycin, clindamycin or rifampicin; penicillins, such as penicillin G, penicillin V, ampicillin, mezlocillin or amoxicillin; polypeptides, such as bacitracin or polymyxin; tetracyclines, such as tetracycline, chlorotetracycline, oxytetracycline, minocycline or doxycycline; carbapenems, such as imipenem, loracarbef, meropenem or panipenem; cephalosporins, such as cefalexin, cefoxitin, cefuroxime axetil, cefotaxime, cefpodoxim proxetil, cefaclor, cefadroxil or cephalothin; gyrase inhibitors, such as ciprofloxacin, norfloxacin, ofloxacin or pefloxacin, or other different antibiotics, such as chloramphenicol.

Particularly worthy of mention in this connection

is also the conjoint administration of pantoprazole with a plurality of antimicrobially-active ingredients, for example with a combination of bismuth salt and/or tetracycline with metronidazole, or with the combination of amoxicillin or clarithromycin with metronidazole.

Antimicrobially-active ingredients which may be emphasized are erythromycin, azithromycin, clarithromycin, clindamycin, rifampicin, ampicillin, mezlocillin, amoxicillin, tetracycline, minocycline, doxycycline, imipenem, meropenem, cefalexin, cefuroxime axetil, cefpodoxime proxetil, cefaclor, cefadroxil, ciprofloxacin, norfloxacin, ofloxacin and pefloxacin.

Clarithromycin and amoxicillin may be mentioned as antimicrobially-active ingredients which should be particularly emphasized.

Combined administration means, for the purpose of the present invention, fixed and, in particular, free combinations, i.e. either slow-release pantoprazole and the antimicrobially-active ingredient are present together in one dosage unit, or slow-release pantoprazole and antimicrobially-active ingredient, which are present in separate dosage units, are administered in direct succession or at a relatively large time interval; a relatively large time interval means a time span up to a maximum of 24 hours. For use as separate dosage units, these are preferably made available together in one pack. For example, the two dosage units are packed together in blister packs which are designed with regard to the relative arrangement of the two dosage units with respect to one another, the inscription and/or coloring in a manner known per se so that the times for taking the individual components (dosage regimen) of the two dosage units are evident to a patient.

A dosage unit means, in particular, a medicinal dosage form in which slowing of pantoprazole release is achieved with as few problems as possible. This includes, in particular, tablets, coated tablets or pellets, and microtablets in capsules, with the dosage form advantageously being designed so that the two active-ingredient components (pantoprazole on the one hand and antimicrobially-active ingredient on the other hand) are

released, or made available effectively for the body, in such as way that an optimal active ingredient profile, and thus action profile, is achieved.

It is possible to use (for retarding release) various types and degrees of retardation so that a pantoprazole plasma level, which persists as long as possible and is sufficient for raising pH, is ensured.

The pharmaceutical formulation of the antimicrobially-active ingredient is carried out as is familiar per se to the skilled worker for the individual active ingredient.

Rapid release of part of the pantoprazole and extending release of another part can be achieved, for example, also by layered tablets or multilayer tablets, in which case part of the pantoprazole is present in an outer coating in a form without retarding its release; this is followed by another coating containing the antimicrobially-active ingredient and then the core with the pantoprazole, whose release is extended in a suitable manner.

The details of how to achieve slowing of or extending release are familiar to the skilled worker on the basis of his expert knowledge. The skilled worker is likewise familiar with suitable ancillary substances and vehicles for the required dosage forms (pharmaceutical formulations). Besides solvents, tablet auxiliary substances and other active ingredient excipients it is possible to use, for example, tablet-coating compositions, plasticizers, antioxidants, preservatives, dyes, etc. Where incompatibilities between the active ingredients or between the active ingredients and ancillary substances are expected, suitable separating layers are provided where appropriate (for example in layered or multi-layer tablets).

The dosage of the active ingredients depends greatly on the nature of the antimicrobially-active ingredients used. A typical dosage for pantoprazole can be regarded as being a daily dose of from about 0.01 to about 20, preferably from 0.05 to 5, in particular from 0.1 to 1.5, mg/kg of body weight, where appropriate in the form of a plurality of single doses. Penicillins, such as amoxicillin, are administered in a daily

dose of from about 5 to 40, preferably from 10 to 20, mg/kg of body weight.

Because of a great tendency to decompose in a neutral and, in particular, acidic environment, which also results in highly colored decomposition products, for oral compositions, it is necessary on the one hand to keep pantoprazole in an alkaline environment and, on the other hand, to protect it from exposure to acids. It is generally known to coat tablets or pellets which contain an acid-labile active ingredient with an enteric coating which, after passage through the stomach, rapidly dissolves in the alkaline medium in the intestine. In the case of pantoprazole, which is very acid-labile, it is necessary to process it in the tablet core or in pellets in the form of its alkaline salts, for example as sodium salts, or together with alkaline substances. Since the substances suitable for enteric coatings contain free carboxyl groups, a problem arises when the enteric coating is partly or even completely dissolved from the inside because of the alkaline medium in the interior, and the free carboxyl groups promote decomposition of the active ingredients. It is therefore necessary to provide a sealing intermediate layer (subcoating) between the enteric coating and the alkaline tablet core. EP-A 0244380 proposes to coat cores which contain the active ingredient together with alkaline compounds or as alkaline salt with at least one layer, which is soluble in water or rapidly disintegrates in water, of nonacidic, inert pharmaceutically-acceptable substance before the enteric layer is applied.

The intermediate layer or intermediate layers act as pH-buffering zones in which hydrogen ions, which diffuse in from the outside, are able to react with the hydroxyl ions which diffuse out of the alkaline core. In order to increase the buffer capacity of the intermediate layer, it is proposed to incorporate buffer substance into the intermediate layer(s). It is possible in practice by this method to obtain rather stable compositions. However, relatively thick intermediate layers are required to prevent the unsightly discoloration which occurs even on only slight decomposition. In addition, considerable effort

must be made to avoid traces of moisture during manufacture.

It is a further aim within the scope of the present invention to provide an oral pharmaceutical composition with delayed and controlled release of active ingredients in pellet or tablet form for pantoprazole, which is distinguished by great resistance to decomposition and discoloration of the active ingredient caused by moisture and other effects.

This aim is particularly advantageously achieved by providing at least one release-slowing intermediate layer of water-insoluble film former, which at the same time represents a barrier for mutual interactions between the active ingredient with an alkaline reaction and the enteric coating with an acidic reaction.

In this connection, film formers are regarded as insoluble in water when they cannot be dissolved in water without further additions (organic solvents, detergents, alkalizing substances, etc.).

The invention therefore also relates to an oral pharmaceutical composition in pellet or tablet form for acid-labile irreversible proton pump inhibitors comprising an alkaline pellet or tablet core, at least one release-slowing, release-controlling intermediate layer and an outer enteric layer which is soluble in the small intestine, wherein the intermediate layer for the pharmaceutical composition is formed from a water-insoluble film former, the film former being applied from anhydrous solution or aqueous dispersion.

The slowing of release can be achieved, for example, by a semipermeable membrane, as disclosed in numerous patents (e.g. EP B 0185331).

The details of how to achieve slowing of release are familiar to the skilled worker on the basis of his expert knowledge. The skilled worker is likewise familiar with suitable ancillary substances and vehicles for the required dosage forms (pharmaceutical formulations). Besides solvents, tablet ancillary substances and other active ingredient excipients it is possible to use, for example, tablet-coating compositions, plasticizers, antioxidants, preservatives, dyes, etc. Where

incompatibilities between the active ingredients or between the active ingredients and ancillary substances are expected, suitable separating layers are provided where appropriate.

The oral pharmaceutical compositions according to the invention are distinguished from the prior art by controlled release of active ingredients and increased stability. It is particularly advantageous to keep the intermediate layer (which controls the release of active ingredients) very thin (between 20 and 80, preferably between 40 and 60, μm), which leads to a considerable saving of material and shorter processing times. The insolubility of the intermediate layer in water means that the application of the enteric layer in the form of aqueous suspensions is not critical because there can be no dissolution of the intermediate layer. Furthermore, oral pharmaceutical compositions with a considerably smoother surface are obtained, which not only leads to a better visual appearance but also technically simplifies an imprinting process for tablets.

For a basic reaction of the pellet or tablet core it is mixed (where required increase in pH is not achieved simply by using an active-ingredient salt) with an inorganic base. Mention may be made in this connection of, for example, the pharmacologically-suitable alkali-metal, alkaline-earth-metal or earth-metal salts of weak acids and the pharmacologically-suitable hydroxides and oxides of alkaline-earth and earth metals. Sodium carbonate may be mentioned as a base to be emphasized by way of example.

Besides filler and binder, other ancillary substances, in particular lubricants and nonstick agents, and tablet disintegrants, are used in the manufacture of the tablet cores. A suitable binder is, in particular, polyvinylpyrrolidone in various degrees of polymerization. Examples of lubricants and nonstick agents which may be mentioned are higher fatty acids and their alkali-metal and alkaline-earth-metal salts, such as calcium stearate. Suitable tablet disintegrants are, in particular, chemically inert agents. Tablet disintegrants which may be mentioned as preferred are crosslinked polyvinylpyrrolidone, crosslinked sodium carboxymethylcelluloses

and sodium starch glycolate.

Examples of film-forming polymers which can be used in the water-insoluble release-slowing intermediate layer(s) (to be applied to the pellet or tablet core) include ethylcellulose, polyvinyl acetate, ammonio methacrylate copolymer type A (e.g. Eudragit® RL) and type B (Eudragit® RS) etc. The release rate can be controlled not only by incorporating therein suitable water-soluble pore formers, such as PEG, lactose, mannitol, sorbitol, HPMC, etc., but also by the thickness of the coating layer applied.

The solvents or dispersants used for the release-controlling polymer dispersion are non-aqueous organic solvents, such as alcohols, ketones or halogenated hydrocarbons or mixtures of such solvents.

It is possible in a similar way to use osmotic systems with semipermeable membranes of cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, as described in US-A 3845770, US-A 3916899, US-A 4036227, US-A 4093708, US-A 4096238, US-A 4135514 and US-A 4142526, to control the release of active ingredients. These can be coated with aqueous dispersions of enteric lacquers without changing release rate.

Examples of suitable polymers for the enteric coating are methacrylic acid/methyl methacrylate copolymer or methacrylic acid/ethyl methacrylate copolymer (Eudragit® L) or cellulose derivatives, such as carboxymethylethylcellulose (CMEC, Duodcel), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropylmethylcellulose phthalate (HP50, HPSS), hydroxypropylmethylcellulose acetate succinate (HPMCAS) or polyvinyl acetate phthalate, to which it is also possible to add, if desired, plasticizer (such as propylene glycol) and/or other additives and ancillary substances (e.g. buffers, bases, such as, preferably, aluminum hydroxide, or pigments).

The layers are applied in conventional ways using equipment customary for these purposes.

Examples

The following formulation examples explain the invention in detail without restricting it.

Example 1

Tablets:

I. Production of uncoated core:

a) Pantoprazole Na x 1.5 H ₂ O	45.1 mg
b) Sodium carbonate	10.0 mg
c) Mannitol	20.0 mg
d) HPMC 2910 3 cps	25.0 mg
e) HPMC 2910 15 cps	4.0 mg
f) Calcium stearate	2.1 mg
	<hr/> 106.2 mg

a) is mixed with one part of b), c) and d). The remainder of b) and c) is added to the clear aqueous solution of e), and the pH is adjusted to > 10 with b). This solution is used for fluidized bed granulation. The remainder of d) and f) is added to the dried granules, and the granules are compressed in a suitable tableting machine.

II. Release-slowing layer

g) Ethylcellulose	9.85 mg
h) Lactose micronized	2.37 mg
i) Propylene glycol	0.98 mg
j) Ammonia 25%	0.80 mg
	<hr/> 14.00 mg

g) is dissolved in 165 ml of isopropanol to prepare solution (A). A fine suspension of h) in 165 ml of isopropanol is prepared using a rotor-stator agitator, and subsequently i) and j) are stirred in using a suitable agitator to prepare suspension (B). The solution (A) and the suspension (B) are combined.

The tablet cores obtained from I are coated to an adequate layer thickness with the suspension obtained above in suitable apparatus.

III. Enteric coating:

l) Eudragit® L	13.64 mg
m) Triethyl citrate	1.36 mg
	<hr/> 15.00 mg

l) is diluted with 140 ml of water, and m) is added. The resulting dispersion is screened before processing. The dispersion from III is sprayed onto the presealed cores obtained from II in suitable equipment.

Example 2

Tablets:

I. Production of the uncoated core:

Production of the cores took place as in Example I point I.

II. Release-slowing layer:

g)	Polyvinyl acetate	9.15 mg
h)	Lactose micronized	2.27 mg
i)	Propylene glycol	0.91 mg
j)	Ammonia 25%	0.80 mg
		<hr/>
		13.13 mg

g) is dissolved in 150 ml of a 1:1 acetone/chloroform mixture to prepare a solution (A).

A fine dispersion of h) in 150 ml of a 1:1 acetone/chloroform mixture is prepared using a rotor-stator agitator, and subsequently i) and j) are stirred in using a suitable agitator to prepare a suspension (B). Solution (A) and suspension (B) are combined.

The tablet cores obtained in I are coated to a sufficient layer thickness with the suspension obtained above in suitable apparatus.

III. Enteric coating:

1)	Eudragit® L	13.46 mg
m)	Triethyl citrate	1.36mg
		<hr/>
		15.00 mg

Total weight per enteric film-coated

tablet 183.50 mg

1) is diluted with 135 ml of water, and m) is added.

The dispersion is screened before processing.

The dispersion from III is sprayed onto the presealed cores obtained in II in suitable equipment.

Example 3

Pellets:

I. Starter Pellets

a)	Sucrose pellets (0.7-0.85 mm)	950.0 g
b)	Hydroxypropylmethylcellulose 2910 (USP)	40.0 g
c)	Propylene glycol	9.9 g
d)	NaOH	0.1 g

a) is sprayed with an aqueous solution of b), c) and d) in a fluidized bed (Wurster method).

II. Active pellets

e)	Pantoprazole Na x 1.5 H	403.0 g
f)	Hydroxypropylmethylcellulose 2910 (USP)	403.0 g
g)	Propylene glycol	201.5 g
h)	NaOH	1.0 g

f), g), h), e) are successively dissolved in 4 liters of purified water and sprayed onto 900 g of the pellets obtained in I in a fluidized bed (Wurster method).

III. Presealed pellets

A release-slowing layer is applied in analogy to the procedure described for tablets in a pan or fluidized bed.

IV. Enteric-coated pellets

The coating is applied in analogy to the procedure described for the tablets in a pan or fluidized bed.

The pellets are subsequently packed into capsules of suitable size (e.g. size 1).

Example 4

Pellets:

I. Active Pellets

c)	Pantoprazole Na x 1.5 H ₂ O	403.0 g
d)	Na carbonate	87.3 g
e)	Microcrystalline cellulose	
	(Avicel PH101)	117.0 g
f)	Na carboxymethylcellulose	18.0 g

c) - f) are premixed dry and subsequently moistened to a paste-like consistency with a solution of Na carbonate and Na carboxymethylcellulose in water in a conventional kneader or high-speed mixer. The resulting composition is then extruded and shaped into pellets by the extruder/rounder

method familiar to the skilled worker. The moistened pellets are dried in suitable equipment (drying oven, fluidized bed, etc.).

III. Release-slowing layer:

The release-slowing layer is applied in analogy to the procedure described for tablets in a pan or fluidized bed.

IV. Enteric-coated pellets

The coating is applied in analogy to the procedure described for tablets in a pan or fluidized bed.

The pellets are subsequently packed into capsules of suitable size (e.g. size 1).

The invention and its advantages are readily understood from the foregoing description. As is apparent, various changes can be made in the products and methods without departing from the spirit and scope of the invention or sacrificing its material advantages. The products and processes hereinbefore described are merely illustrative of a preferred embodiments of the invention.

WHAT IS CLAIMED IS:

1. An oral pharmaceutical composition for treating a disorder caused by *Helicobacter* comprising pantoprazole in combination with at least one antimicrobially-active ingredient, wherein at least part of the pantoprazole is in slow-release form.

2. An oral pharmaceutical composition as claimed in claim 1, wherein the pantoprazole, which is wholly or partly in slow-release form is in fixed combination with at least one antimicrobially-active ingredient in a single dosage unit.

3. An oral pharmaceutical composition as claimed in claim 2, wherein the pantoprazole is in pellet form together with at least one antimicrobially-active ingredient in a capsule as a dosage unit.

4. An oral pharmaceutical composition as claimed in claim 2, wherein the pantoprazole, which is wholly or partly in slow-release form is together with at least one antimicrobially-active ingredient in a multilayer tablet.

5. An oral pharmaceutical composition as claimed in claim 1, wherein the pantoprazole and at least one antimicrobially-active ingredient are in separate dosage units in a single package.

6. An oral pharmaceutical composition as claimed in claim 5, wherein the single package is a blister pack which is designed by the relative arrangement of individual components of the dosage units, by inscription and/or by coloring to communicate the dosage regimen to a patient.

7. An oral pharmaceutical composition as claimed in claim 1, wherein the slow-release form of pantoprazole has an alkaline pellet or tablet core, at least one intermediate layer controlling release of active ingredient, and an outer enteric layer which is soluble in the small intestine.

8. An oral pharmaceutical composition as claimed in claim 7, wherein at least one intermediate layer is formed from a water-insoluble, release-slowing film former.

9. An oral pharmaceutical composition as claimed in claim 8, wherein the film former has been applied from a solution or dispersion.

10. An oral pharmaceutical composition as claimed in claim 8, wherein the intermediate layer contains, as water-insoluble, release-slowing film former, water-insoluble cellulose ether and/or polyvinyl acetate.

11. An oral pharmaceutical composition as claimed in claim 8, wherein the intermediate layer contains, as water-insoluble, release-slowing film former, ethylcellulose, ammonio methacrylate copolymer (Eudragit® RS, Eudragit® RL) or polyvinyl alcohol.

12. An oral pharmaceutical composition as claimed in claim 11, wherein the outer enteric layer, which is soluble in the small intestine, comprises methacrylic acid/methyl methacrylate copolymer or methacrylic acid/ethyl methacrylate copolymer (Eudragit® L).

13. An oral pharmaceutical composition as claimed in claim 7, wherein the outer enteric layer comprises a cellulose-derivative coating.

14. An oral pharmaceutical composition as claimed in claim 13, wherein the cellulose derivative is a member selected from the group consisting of a carboxymethylethylcellulose, cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropylmethylcellulose phthalate and hydroxypropylmethylcellulose acetate succinate.

15. An oral pharmaceutical composition as claimed in claim 7, wherein a member selected from the group consisting of a pore former, plasticizer, buffer, base and pigment is additionally present in the intermediate layer.

16. A pharmaceutical as claimed in claim 1, wherein the antimicrobially-active ingredient is a member selected from the group consisting of bismuth subcitrate, bismuth subsalicylate, nitrofurazone, nitrofurantoin, furazolidone, metronidazole, tinidazole, nimorazole, gentamicin, neomycin, kanamycin, amikacin, streptomycin, erythromycin, azithromycin, clarithromycin, clindamycin, rifampicin, penicillin G, penicillin V, ampicillin, mezlocillin, amoxicillin, bacitracin, polymyxin, tetracycline, chlorotetracycline, oxytetracycline, minocycline, doxycycline, imipenem, loracarbef, meropenem, panipenem, cefalexin, cefoxitin, cefuroxime axetil, cefotaxime, cefpodoxime proxetil, cefaclor, cefadroxil, cephalothin, ciprofloxacin, norfloxacin, ofloxacin, pefloxacin and chloramphenicol.

17. The use of pantoprazole in combination with at least one antimicrobially-active ingredient for the preparation of a pharmaceutical composition for the treatment of disorders caused by *Helicobacter* wherein at least part of pantoprazole is in slow-release form.

18. A process for producing an oral pharmaceutical composition in pellet or tablet form for pantoprazole, as active ingredient, or for combined use thereof with at least one antimicrobially-active ingredient for treating a disorder caused by Helicobacter, which comprises a) incorporating the active ingredient as an alkaline salt and/or with addition of an alkaline substance in a pellet or tablet core, b) applying thereto at least one release-slowing intermediate layer essentially comprising a water-insoluble, release-slowing acidic film former and c) subsequently applying an outer enteric layer which is soluble in the small intestine.

INTERNATIONAL SEARCH REPORT

International Application No
PL 1/EP 96/02892

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/28 A61K9/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,92 03135 (SMITH, KLINE & FRENCH) 5 March 1992 see claims 1-6 see page 2, line 11 - line 20 see page 3, line 29 - line 33 see page 4, line 34 - page 5, line 10 ---	1-3,5,6, 15-17
Y	WO,A,94 24867 (SEPRACOR INC.) 10 November 1994 see claims 1,2 see page 13, line 4 - line 17 see page 14, line 17 - line 23 see example 3 --- -/--	1-3,5,6, 15-17

☒ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

15 November 1996

Date of mailing of the international search report

28. 11. 96

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/02892

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>EP,A,0 519 365 (BYK GULDEN LOMBERG) 23 December 1992 cited in the application see claims 1,4 see page 2, line 56 - page 3, line 9 see examples 1,2 -----</p>	7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 96/02892

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/28, 9/50	A1	(11) International Publication Number: WO 97/02021 (43) International Publication Date: 23 January 1997 (23.01.97)
(21) International Application Number: PCT/EP96/02893 (22) International Filing Date: 2 July 1996 (02.07.96) (30) Priority Data: 08/498,391 5 July 1995 (05.07.95) US (71) Applicant: BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH [DE/DE]; Byk-Gulden-Strasse 2, D-78467 Konstanz (DE). (72) Inventors: DIETRICH, Rango; Im Tiergarten 16, D-78465 Konstanz (DE). SACHS, George; 17986 Boris Drive, Encino, CA 91316 (US). POSTIUS, Stefan; Austrasse 4b, D-78467 Konstanz (DE). NEY, Hartmut; Peter-Thumb-Strasse 46, D-78464 Konstanz (DE). SENN-BILFINGER, Jörg; Söntistrasse 7, D-78464 Konstanz (DE).		(81) Designated States: AU, BG, BR, BY, CA, CN, CZ, EE, HU, IL, JP, KR, LT, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: ORAL PHARMACEUTICAL COMPOSITIONS WITH DELAYED RELEASE OF REVERSIBLE PROTON PUMP INHIBITORS (57) Abstract An oral pharmaceutical composition of a reversible proton pump inhibitor in pellet or tablet form, wherein the reversible proton pump inhibitor is at least partly in slow-release form, is distinguished, on combined administration with an antimicrobially-active ingredient, by an enhanced action of rapid onset against disorders caused by Helicobacter.		

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ORAL PHARMACEUTICAL COMPOSITIONS WITH DELAYED RELEASE
OF REVERSIBLE PROTON PUMP INHIBITORS

Field of the Invention

The present invention relates to oral pharmaceutical compositions in pellet or tablet form for reversible proton pump inhibitors for combined use with antimicrobially-active ingredients for the treatment of disorders caused by *Helicobacter*.

Prior Art

Control of the microbe *Helicobacter pylori*, which is thought to be responsible for certain gastric disorders, by combined use of an antimicrobially-active ingredient which is active against *Helicobacter pylori* and of an agent which reduces gastric acid has been regarded as the method of choice for some time.

Besides inhibitors of gastric acid secretion of the H_2 receptor antagonist type, in recent times use has been made, with more or less success, of compounds of the class of so-called irreversible proton pump inhibitors (such as pantoprazole, omeprazole or lansoprazole). Irreversible proton pump inhibitors are substances which covalently, and thus irreversibly, bind to the enzyme which is responsible for acid secretion in the stomach, the H^+/K^+ ATPase.

Besides so-called irreversible proton pump inhibitors, which essentially have a common basic chemical structure (pyridinylmethylsulfinylbenzimidazoles), there are the so-called reversible H^+/K^+ ATPase inhibitors which have different basic chemical structures and which, as the name indicates, reversibly bind to the enzyme responsible for gastric acid secretion. These are called reversible proton pump inhibitors in connection with the present invention. Reversible proton pump inhibitors are

disclosed, for example, in the documents DE-A-3917232, EP-A-0399267, EP-A-0387821, JP-A-3031280, JP-A-2270873, EP-A-0308917, EP-A-0268989, EP-A-0228006, EP-A-0204285, EP-A-0165545, EP-A-0125756, EP-A-0120589, EP-A-0509974, DE-A-3622036, EP-A-0537532, EP-A-0535529, JP-A-3284686, JP-A-3284622, US-P-4,833,149, EP-A-0261912, WO-A-9114677, WO-A-9315055, WO-A-9315071, WO-A-9315056, WO-A-9312090, WO-A-9212969, WO-A-9118887, EP-A-0393926, EP-A-0307078, US-P-5,041,442, EP-A-0266890, WO-A-9414795, EP-A-0264883, EP-A-0033094, EP-A-0259174, EP-A-0330485, WO-A-8900570, EP-A-0368158, WO-A-9117164, WO-A-9206979, WO-A-9312090, WO-A-9308190, WO-A-9418199, DE-A-3011490, US-P-4,464,372, EP-A-0068378 and WO-A-9424130.

Combined use of reversible proton pump inhibitors with antimicrobially-active ingredients has a good effect against *Helicobacter* in vitro. However, the clinical effect achieved with this combined use is disappointing.

Summary of the Invention

The action of an antimicrobially-active ingredient on *Helicobacter* is surprisingly enhanced by administering a reversible proton pump inhibitor in slow-release dosage form (extended release form). It must be regarded as particularly surprising that, in addition, administration of the slow-release reversible proton pump inhibitor results in the onset of action taking place significantly faster than on administration of a non-slow-release reversible proton pump inhibitor. The duration of treatment until *Helicobacter* is eradicated is shortened, saving considerable amounts of antibiotic and acid inhibitor.

The invention thus relates to an oral pharmaceutical composition for treating a disorder caused by *Helicobacter* comprising a reversible proton pump inhibitor in combination with at least one antimicrobially-active ingredient, wherein at least part of the reversible proton pump inhibitor is in slow-release form. Further subject-matters are evident from the claims.

Details

Reversible proton pump inhibitors are, for the purpose of the present invention, those active ingredients which reversibly bind to the enzyme responsible for gastric acid secretion, H^+/K^+ ATPase. Examples of reversible proton pump inhibitors are enumerated in the previously-noted documents. Examples of reversible proton pump inhibitors are, e.g., 8-(2-methoxycarbonylamino-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine (hereinafter B9401-011), 3-hydroxymethyl-8-(2-methoxycarbonylamino-6-methylbenzyloxy)-2-methylimidazo[1,2-a]pyridine, 3-hydroxymethyl-8-(2-methoxycarbonylamino-6-methylbenzyloxy)-2-methylimidazo[1,2-a]pyridine, 8-(2-methoxycarbonylamino-6-methylbenzyloxy)-2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-tert-butoxycarbonylamino-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-tert-butoxycarbonylamino-6-methylbenzyloxy)-2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-ethoxycarbonylamino-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-isobutoxycarbonylamino-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-isopropoxycarbonylamino-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-tert-butoxycarbonylamino-6-methylbenzylamino)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine, 8-(2-tert-butoxycarbonylamino-6-methylbenzyloxy)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine, 8-(2-[(2-methoxyethoxy) carbonylamino]-6-methylbenzyloxy)-2-methylimidazo[1,2-a]pyridine-3-methanol, 8-(2-[(2-methoxyethoxy) carbonylamino]-6-methylbenzylamino)-2-methylimidazo[1,2-a]pyridine-3-methanol, 8-(2-[(2-methoxyethoxy) carbonylamino]-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-[(2-methoxyethoxy) carbonylamino]-6-methylbenzyloxy)-2-methylimidazo[1,2-a]pyridine-3-methanol, 8-(2-[(2-methoxyethoxy) carbonylamino]-6-methylbenzyloxy)-2,3-dimethylimidazo[1,2-a]pyridine, 3-hydroxymethyl-2-methyl-8-benzyloxyimidazo-[1,2-a]pyridine, 3-hydroxymethyl-2-trifluoromethyl-8-benzyloxyimidazo-[1,2-a]pyridine, 1,2-dimethyl-3-cyanomethyl-8-benzyloxyimidazo[1,2-a]pyridine, 2-methyl-3-cyanomethyl-8-

benzyloxyimidazo[1,2-a]pyridine, 3-butyryl-8-methoxy-4-(2-methylphenylamino)quinoline and 3-butyryl-8-hydroxyethoxy-4-(2-methylphenylamino) quinoline.

Reversible proton pump inhibitors can, in this connection, be present as such, in the form of their salts and/or their solvates (e.g. hydrates), etc. Particularly suitable salts are (because all reversible proton pump inhibitors are substances with a basic reaction) all acid-addition salts. Particular mention may be made of the pharmacologically-acceptable salts of inorganic and organic acids customarily used in pharmaceutical technology, including water-soluble and water-insoluble acid-addition salts with acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid and 3-hydroxy-2-naphthoic acid, the acids being used in the preparation of the salt in a ratio of amounts which are equimolar or different therefrom - depending on whether the acid is mono- or polybasic and depending on the salt required.

Examples of suitable antimicrobially-active ingredients (active against *Helicobacter pylori*) are enumerated in European Patent Application EP-A-282131. These active ingredients include, for example, bismuth salts (such as bismuth subcitrate or bismuth subsalicylate), sulfonamides, nitrofurans (such as nitrofurazone, nitrofurantoin or furazolidone), metronidazole, tinidazole, nimorazole or antibiotics. Examples of antibiotics which may be mentioned in this connection are, arranged according to particular classes of active ingredient: aminoglycosides, such as gentamicin, neomycin, kanamycin, amikacin or streptomycin; macrolides, such as erythromycin, azithromycin, clarithromycin, clindamycin or rifampicin; penicillins, such as penicillin G, penicillin V, ampicillin, mezlocillin or amoxicillin; polypeptides, such as bacitracin or polymyxin; tetracyclines, such as tetracycline, chlorotetracycline,

oxytetracycline, minocycline or doxycycline; carbapenems, such as imipenem, loracarbef, meropenem or panipenem; cephalosporins, such as cefalexin, cefoxitin, cefuroxime axetil, cefotaxime, cefpodoxime proxetil, cefaclor, cefadroxil or cephalothin; gyrase inhibitors, such as ciprofloxacin, norfloxacin, ofloxacin or pefloxacin; or other different antibiotics, such as chloramphenicol. Particularly worthy of mention in this connection is also the combination of a plurality of antimicrobially-active ingredients, for example the combination of a bismuth salt and/or tetracycline with metronidazole, or the combination of amoxicillin or clarithromycin with metronidazole.

Particularly worthy of mention in this connection is also administration of a reversible proton pump inhibitor together with a plurality of antimicrobially-active ingredients, for example with the combination of a bismuth salt and/or tetracycline with metronidazole, or with the combination of amoxicillin or clarithromycin or with metronidazole.

The dosage of the active ingredients depends greatly on the nature of the reversible proton pump inhibitor used and of the antimicrobially-active ingredient(s) used. A typical dosage of a reversible proton pump inhibitor as disclosed, for example, in WO-A-9418199 can be regarded as a daily dose of from about 0.01 to about 20, preferably from 0.05 to 5, and in particular from 0.1 to 1.5, mg/kg of body weight, where appropriate in the form of a plurality of single doses. Penicillins, such as amoxicillin, are administered in a daily dose of from about 5 to 40, preferably from 10 to 20, mg/kg of body weight.

Antimicrobially-active ingredients which may be emphasized are erythromycin, azithromycin, clarithromycin, clindamycin, rifampicin, ampicillin, mezlocillin, amoxicillin, tetracycline, minocycline, doxycycline, imipenem, meropenem, cefalexin, cefuroxime axetil, cefpodoxime proxetil, cefaclor, cefadroxil, ciprofloxacin, norfloxacin, ofloxacin and pefloxacin.

Clarithromycin and amoxicillin may be mentioned as antimicrobially-active ingredients which should be particularly emphasized.

Combined administration means (for the purpose of the

present invention) fixed and, in particular, free combinations, i.e. the slow-release reversible proton pump inhibitor and the antimicrobially-active ingredient are present together in one dosage unit, or slow-release reversible proton pump inhibitor and antimicrobially-active ingredient, which are present in separate dosage units, are administered in direct succession or at a relatively large time interval; a relatively large time interval means within a time span of up to a maximum of 24 hours. For use as separate dosage units, these are preferably made available together in one pack. For example, the two dosage units are packed together in blister packs which are designed with regard to the relative arrangement of the two dosage units with respect to one another, the inscription and/or coloring in a manner known per se so that the times for taking the individual components (dosage regimen) of the two dosage units are evident to a patient.

A dosage unit means, in particular, those medicinal dosage forms in which slowing or extending of reversible proton pump inhibitor release is achieved with as few problems as possible. These include, in particular, tablets, coated tablets or pellets, and microtablets in capsules, with the dosage form advantageously being designed so that the two active ingredient components (reversible proton pump inhibitor on the one hand and antimicrobially-active ingredient on the other hand) are released, or made available effectively for the body, in such a way that an optimal active-ingredient profile (and thus action profile) is achieved.

For slowing release, various types and degrees of retarding release may be used to ensure a reversible proton pump inhibitor plasma level which persists as long as possible and is sufficient for raising pH.

The pharmaceutical formulation of the antimicrobially-active ingredient(s) is carried out in a manner which is familiar per se to the skilled worker for the individual active ingredients.

The rapid release of part of the reversible proton pump inhibitor and retarding release of another part is optionally achieved, for example, by layered tablets or multilayer tablets,

in which part of the reversible proton pump inhibitor is present in an outer coating in a form without slowing release; this is followed by another coating containing the antimicrobially-active ingredient and then the core with the reversible proton pump inhibitor whose release is slowed in a suitable manner.

The details of how to achieve slowing release are familiar to the skilled worker on the basis of his expert knowledge. The skilled worker is likewise familiar with suitable ancillary substances and vehicles for the required dosage forms (pharmaceutical formulations). Besides solvents, tablet ancillary substances and other active ingredient excipients it is possible to use, for example, tablet-coating compositions, plasticizers, antioxidants, preservatives, dyes, etc. Where incompatibilities between the active ingredients or between the active ingredients and ancillary substances are to be expected, suitable separating layers must be provided where appropriate.

The oral pharmaceutical compositions according to the invention are distinguished from the prior art by controlled release of active ingredients and increased stability.

Besides filler and binder, other ancillary substances, in particular lubricants and nonstick agents, and tablet disintegrants, are used in the manufacture of the tablet cores. A suitable binder is, in particular, polyvinylpyrrolidone in various degrees of polymerization. Examples of lubricants and nonstick agents are higher fatty acids and their alkali-metal and alkaline-earth-metal salts, such as calcium stearate. Suitable tablet disintegrants are, in particular, chemically-inert agents. Preferred tablet disintegrants include cross-linked polyvinylpyrrolidone, crosslinked sodium carboxymethylcelluloses and sodium starch glycolate.

Examples of suitable film-forming polymers, in respect of the water-insoluble release-slowing intermediate layer(s) to be applied to the pellet or tablet core, include ethylcellulose, polyvinyl acetate, ammonio methacrylate copolymer type A (e.g. Eudragit® RL) and type B (Eudragit® RS) etc. The release rate can be controlled not only by incorporating suitable water-soluble pore formers such as PEG, lactose, mannitol, sorbitol, HPMC, etc., but also by the thickness of the coating layer applied.

The solvents or dispersants used for the release-controlling polymer dispersion are non-aqueous organic solvents, such as alcohols, ketones, halogenated hydrocarbons or mixtures of such solvents.

It is possible in a similar way to use osmotic systems with semipermeable membranes of cellulose acetate, cellulose acetate butyrate or cellulose acetate propionate (as described in US-A 3845770, US-A 3916899, US-A 4036227, US-A 4093708, US-A 4096238, US-A 4135514 and US-A 4142526) to control the release of active ingredients. These can be coated with aqueous dispersions of enteric lacquers without changing the release rate.

Examples of suitable polymers for the enteric coating are methacrylic acid/methyl methacrylate copolymer or methacrylic acid/ethyl methacrylate copolymer (Eudragit® L) or cellulose derivatives, such as carboxymethylethylcellulose (CMEC, Duodcel), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropylmethylcellulose phthalate (HP50, HP55), hydroxypropylmethylcellulose acetate succinate (HPMCAS) or polyvinyl acetate phthalate, to which it is also possible to add, if desired, plasticizer (such as propylene glycol) and/or other additives and ancillary substances (e.g. buffer; base, such as, preferably, aluminum hydroxide; or pigment). The layers are applied in conventional ways using equipment customary for these purposes.

Susceptibility of Commercial Application

The combined use according to the invention of a slow-release reversible proton pump inhibitor with an antimicrobially-active ingredient meets all the requirements for a pharmaceutical product or combination pharmaceutical product for the treatment of gastric disorders attributable to the microbe, *Helicobacter pylori*. The particular advantages connected with the combined use of the slow-release drug form with an antimicrobially-active ingredient which may be mentioned are: the rapid onset of action with pH values as far as neutral in the lumen of the stomach and in the wall of the stomach and an optimal displaying of the effect of the antimicrobially-active ingredient. The

short duration of treatment which can be achieved increases the compliance, which is extremely important for antibiotic treatments.

Examples

The following formulation examples explain the invention in detail without restricting it.

Example 1

Tablets:

I. Production of uncoated core:

a)	B9401-011 (hemimalate)	119.8 mg
b)	Sodium carboxymethylstarch	21.0 mg
c)	Microcrystalline cellulose (e.g.: Avicel PH 101)	21.0 mg
d)	Maize starch	19.4 mg
e)	Magnesium stearate	5.0 mg
		<hr/>
		186.2 mg

a) is mixed with b), c) and part of d). A paste is prepared with the remainder of d). The latter is used for granulation of the powder mixture in a suitable mixer. The granules are dried in a drying oven or fluidized bed. e) is added to the dried granules, and the granules are compressed in a suitable tabletting machine.

II. Release-slowing layer

f)	Ethylcellulose	9.85 mg
g)	Lactose micronized	2.37 mg
h)	Propylene glycol	0.98 mg
		<hr/>
		14.00 mg

f) is dissolved in 165 ml of isopropanol. h) is stirred in for a sufficient length of time using a suitable agitator to form a solution (A). g) is suspended in 165 ml of isopropanol using a rotor-stator agitator to form a fine suspension (B). (A) and (B) are combined.

The tablet cores obtained under I are coated to an adequate layer thickness with the suspension obtained above in suitable apparatus.

Example 2

Tablets:

I. Production of uncoated core:

Production of the cores takes place as in Example 1, I.

II. Release-slowing layer:

f)	Polyvinyl acetate	10.38 mg
g)	Lactose micronized	2.59 mg
h)	Propylene glycol	1.03 mg
		<hr/>
		13 .13 mg

f) is dissolved in 150 ml of a 1:1 acetone/chloroform mixture. h) is stirred in for a sufficient length of time, using a suitable agitator to prepare a solution (A).

g) is suspended in 150 ml of a 1:1 acetone/chloroform mixture, using rotor-stator agitator to prepare a fine dispersion (B). (A) and (B) are combined.

The tablet cores obtained under I are coated to a sufficient layer thickness with the thus-obtained dispersion in suitable apparatus.

Example 3

Pellets:

I. Starter pellets

a)	Sucrose pellets (0.7-0.85 mm)	950.0 g
b)	Hydroxypropylmethylcellulose 2910 (USP)	40.0 g
c)	Propylene glycol	10.0 g

a) is sprayed with an aqueous solution of
b) and c) in a fluidized bed (Wurster method).

II. Active pellets

d)	B9401-011 (Hemimalate)	403.0 g
e)	Hydroxypropylmethylcellulose 2910 (USP)	403.0 g
f)	Propylene glycol	201.5 g

d), e) , f) are successively dissolved in 4 liters of purified water and sprayed onto 900 g of the pellets obtained under I in a fluidized bed (Wurster method).

III. Slow-release pellets

A release-slowing layer is applied in analogy to the procedure described for tablets in a pan or fluidized bed.

Example 4

Pellets:

I. Active pellets

a)	B9401-011 (Hemimalate)	403.0 g
b)	Microcrystalline cellulose (Avicel PH101)	117.0 g
c)	Na carboxymethylcellulose	18.0 g

a) and b) are premixed dry and subsequently moistened to a paste-like consistency with a solution of Na carboxymethylcellulose in water in a conventional kneader or high-speed mixer. The resulting composition is then extruded and shaped into pellets by the extruder/rounder method familiar to the skilled worker. The moistened pellets are dried in suitable equipment (drying oven, fluidized bed, etc.).

III. Slow-release pellets:

The release-slowing layer is applied in analogy to the procedure described for tablets in a pan or fluidized bed.

The invention and its advantages are readily understood from the foregoing description. As is apparent, various changes can be made in the products and methods without departing from the spirit and scope of the invention or sacrificing its material advantages. The products and processes hereinbefore described are merely illustrative of preferred embodiments of the invention.

WHAT IS CLAIMED:

1. An oral pharmaceutical composition for treating a disorder caused by Helicobacter comprising a reversible proton pump inhibitor in combination with at least one antimicrobially-active ingredient, wherein at least part of the reversible proton pump inhibitor is in slow-release form.

2. An oral pharmaceutical composition as claimed in claim 1, wherein the reversible proton pump inhibitor, which is wholly or partly in slow-release form, is in fixed combination with at least one antimicrobially-active ingredient in a single dosage unit.

3. An oral pharmaceutical composition as claimed in claim 2, wherein the reversible proton pump inhibitor is in pellet form together with at least one antimicrobially-active ingredient in a capsule as a dosage unit.

4. An oral pharmaceutical composition as claimed in claim 2, wherein the reversible proton pump inhibitor, which is wholly or partly in slow-release form, is together with at least one antimicrobially-active ingredient in a multilayer tablet.

5. An oral pharmaceutical composition as claimed in claim 1, wherein the reversible proton pump inhibitor and at least one antimicrobially-active ingredient are in separate dosage units in a single package.

6. An oral pharmaceutical composition as claimed in claim 5, wherein the single package is a blister pack which is designed by the relative arrangement of individual components of the dosage units, by inscription and/or by coloring to communicate the dosage regimen to a patient.

7. A pharmaceutical as claimed in claim 1, wherein the reversible proton pump inhibitor is a member selected from group consisting of 8-(2-methoxycarbonylamino-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine, 3-hydroxymethyl-8-(2-methoxycarbonylamino-6-methylbenzylamino)-2-methylimidazo[1,2-a]pyridine, 3-hydroxymethyl-8-(2-methoxycarbonylamino-6-methylbenzyloxy)-2-methylimidazo[1,2-a]pyridine, 8-(2-methoxycarbonylamino-6-methylbenzyloxy)-2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-tert-butoxycarbonylamino-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-tert-butoxycarbonylamino-6-methylbenzyloxy)-2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-ethoxycarbonylamino-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-isobutoxycarbonylamino-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-isopropoxycarbonylamino-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-tert-butoxycarbonylamino-6-methylbenzylamino)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine, 8-(2-tert-butoxycarbonylamino-6-methylbenzyloxy)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine, 8-(2-[(2-methoxyethoxy)carbonylamino]-6-methylbenzyloxy)-2-methylimidazo[1,2-a]pyridine-3-methanol, 8-(2-[(2-methoxyethoxy)carbonylamino]-6-methylbenzylamino)-2-methylimidazo[1,2-a]pyridine-3-methanol, 8-(2-[(2-methoxyethoxy)carbonylamino]-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-[(2-methoxyethoxy)carbonylamino]-6-methylbenzyloxy)-2-methylimidazo[1,2-a]pyridine-3-methanol, 8-(2-[(2-methoxyethoxy)carbonylamino]-6-methylbenzyloxy)-2,3-dimethylimidazo[1,2-a]pyridine, 3-hydroxymethyl-2-methyl-8-benzyloxyimidazo[1,2-a]pyridine, 3-hydroxymethyl-2-trifluoromethyl-8-benzyloxyimidazo[1,2-a]pyridine, 1,2-dimethyl-3-cyanomethyl-8-benzyloxyimidazo[1,2-a]pyridine, 2-methyl-3-cyanomethyl-8-benzyloxyimidazo[1,2-a]pyridine, 3-butyryl-8-methoxy-4-(2-methylphenylamino)quinoline and 3-butyryl-8-hydroxyethoxy-4-(2-methylphenylamino)quinoline, or a salt thereof.

8. A pharmaceutical composition as claimed in claim 1, wherein the reversible proton pump inhibitor is a member selected from the group consisting of 8-(2-methoxycarbonylamino-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine, 8-(2-methoxycarbonylamino-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine, and 8-(2-methoxycarbonylamino-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine, or a salt thereof.

9. A pharmaceutical composition as claimed in claim 1, wherein the antimicrobially-active ingredient is a member selected from the group consisting of bismuth subcitrate, bismuth subsalicylate, nitrofurazone, nitrofurantoin, furazolidone, metronidazole, tinidazole, nimorazole, gentamicin, neomycin, kanamycin, amikacin, streptomycin, erythromycin, azithromycin, clarithromycin, clindamycin, rifampicin, penicillin G, penicillin V, ampicillin, mezlocillin, amoxicillin, bacitracin, polymyxin, tetracycline, chlorotetracycline, oxytetracycline, minocycline, doxycycline, imipenem, loracarbef, meropenem, panipenem, cefalexin, cefoxitin, cefuroxime axetil, cefotaxime, cefpodoxime proxetil, cefaclor, cefadroxil, cephalothin, ciprofloxacin, norfloxacin, ofloxacin, pefloxacin and chloramphenicol.

10. The use of a reversible proton pump inhibitor in combination with at least one antimicrobially-active ingredient for the preparation of a pharmaceutical composition for the treatment of disorders caused by *Helicobacter* wherein at least part of the reversible proton pump inhibitor is in slow-release form.

11. A process for producing an oral pharmaceutical composition in pellet or tablet form for a reversible proton pump inhibitor, as active ingredient, or for combined use thereof with at least one antimicrobially-active ingredient for treating a disorder caused by Helicobacter, which comprises a) incorporating the active ingredient into a pellet or tablet core, b) applying thereto at least one release-slowing intermediate layer essentially comprising a water-insoluble, release-slowing acidic film former and c) subsequently applying an outer enteric layer which is soluble in the small intestine.

INTERNATIONAL SEARCH REPORT

International Application No

PC1/EP 96/02893

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/28 A61K9/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO,A,94 18199 (BYK GULDEN LOMBERG) 18 August 1994 cited in the application see claims 1-9 see page 15, paragraph 3 - page 16, paragraph 3 -----</p>	1-11

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Further documents are listed in the continuation of box C.

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Patent family members are listed in annex.

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Date of the actual completion of the international search

2 December 1996

Date of mailing of the international search report

11. 12. 96

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PC 1 / EP 96/02893

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9418199	18-08-94	AU-A- 6039194	29-08-94
		BG-A- 99855	30-04-96
		CA-A- 2156078	18-08-94
		CN-A- 1119863	03-04-96
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		SK-A- 99795	06-12-95
		ZA-A- 9400990	17-08-94

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/107	A1	(11) International Publication Number: WO 97/09964 (43) International Publication Date: 20 March 1997 (20.03.97)
(21) International Application Number: PCT/SE96/01097 (22) International Filing Date: 4 September 1996 (04.09.96) (30) Priority Data: 9503143-1 12 September 1995 (12.09.95) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventor; and (75) Inventor/Applicant (for US only): VON CORSWANT, Chris- tian [SE/SE]; Ringleken 14, S-431 69 Mölndal (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: MICROEMULSIONS FOR USE AS VEHICLES FOR ADMINISTRATION OF ACTIVE COMPOUNDS (57) Abstract A non-toxic oil-in-water or bicontinuous microemulsion as a vehicle for administration of one or more active compounds having a low solubility in water, which microemulsion contains: a polar phase containing water and optionally an agent for obtaining isotonic conditions, and one or more components (modifiers) for adjusting the polarity of the polar phase; a surfactant film modifier; a non-polar phase consisting of at least one pharmaceutically acceptable oil; and a mixture of a hydrophilic surfactant and a hydrophobic surfactant up to 15 % by weight of the total microemulsion, wherein the hydrophobic surfactant is chosen from a group consisting of lecithin, sphingolipids or galacto lipids.		

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MICROEMULSIONS FOR USE AS VEHICLES FOR ADMINISTRATION OF ACTIVE COMPOUNDS

Technical field

5

The present invention relates to a microemulsion used as a pharmaceutically acceptable vehicle for administration of one or more active compounds parenterally but also orally and transdermally, as well as a process for the preparation and use of such a microemulsion.

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The object of the present invention is to provide a vehicle which increases the solubility of compounds having a low solubility in water at the same time as being non-toxic.

Background of the invention and prior art

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Many of the new pharmaceutically active substances which are prepared today have a very low solubility in water. This could be a problem when administered, especially when a substance is to be administered parenterally, e.g. intravenously, intraperitonially, intraarterially, intramuscularly or subcutaneously. In these cases a vehicle which increases the solubility of the active compound is needed. The solubility in water often has to be increased 1000 times to 10 000 times to reach reasonable volumes for administration. The systems used today are;

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- solvents which are possible to mix with water, such as propylene glycol, polyethylene glycol, ethanol e.t.c;

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- surfactants forming aggregate in which the unsoluble substances can be dissolved, for example ethoxylated castor oil, mixed micells of lecithin + bile salts;

- polyethylene oxide derivatives of sorbitan monoesters, diesters and triesters;

- complexing agents such as cyclodextrines;

- emulsions, for example soybean oil + egglecithin.

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All these systems have different drawbacks. Solvents which are possible to mix with water require high concentrations to be effective. The solubilizing capacity of the surfactants and the complexing agent is often insufficient. Emulsions are thermodynamically unstable and also nontransparent which makes it difficult to decide whether the active substance is completely dissolved or not. Microemulsions are on the contrary, thermodynamically stable mixtures that are formed spontaneously without any addition of external energy, e.g. mechanical stirring, heating, ultrasonification e.t.c. Microemulsions are also transparent which make them superior to ordinary emulsions for use as vehicles for administration of pharmaceutically active compounds.

One objective with the present invention is to provide a microemulsion using minimal amounts of surfactants for use as a vehicle suitable for parenteral as well as oral and transdermal administration of one or more pharmaceutically active compounds.

The benefit with a microemulsion is the high solubilization capacity and the fact that it is both thermodynamically stable and translucent. In EP 211 258 a preparation called an "oil-in-water microemulsion" for parenteral administration is described, which consists of pharmaceutically acceptable lipids, lipophilic drugs and mixtures thereof, and a phospholipid emulsifier in an aqueous phase. However, here the microemulsification is achieved by using mechanical energy input, i.e. droplet size reduction via microfluidization. This is not a microemulsion according to usual definition for microemulsions - "a microemulsion is defined as a system of water, oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution" (Danielsson, I., Lindman, B., Colloids and Surfaces, 1981, 3, p. 391). An oil-in-water microemulsion for parenteral administration is described in FR 2 553 661. This microemulsion contains an ionic surfactant and a aliphatic polyol or an aromatic alcohol having at least 4 carbon atoms as a co-surfactant. In the example of this specification the ratio lipophilic phase : surfactant is 1 : 1. In WO 92/18147 a water-in-oil microemulsion is described which readily converts to an oil-in-water emulsion or microemulsion by the addition of aqueous fluid. This microemulsion contains a hydrophilic water-soluble active

substance. However, it is most likely impossible to use as low amount of surfactant as stated in the claims since there is a need for some kind of surfactant modifier to lower the amount of surfactant. Furthermore, US 4 712 239 describes multicomponent systems for use in pharmaceutical products, which systems comprising an oil, a nonionic surfactant with a hydrophilic-lipophilic balance above 8 and a cosurfactant which is a partial ether or ester of a polyhydroxyl alcohol and a (C₆₋₂₂)fatty alcohol or acid. Optionally an aqueous phase is used and the therapeutic agent may be lipophilic or hydrophilic. Such systems are said to give enhanced transdermal delivery characteristics. In example 1, formulations X and XI contain isopropanol which make the formulations inappropriate for parenteral administration. Furthermore, it is to be noted that in example 1, formulation I the ratio of the medium-chain triglyceride to the caprylic-capric acid glycerol partial esters is 1:1.5. Also WO 93/02664 describes a microemulsion but it is in the form of a water-in-oil microemulsion. Among others it includes a water-soluble therapeutic agent. In EP 334 777 a microemulsion for parenteral or oral administration of cosmetics or pharmaceuticals is disclosed consisting of one polar and one lipid phase and using a mixture of surfactants based upon polyethylene glycol and polyglycerol. The amount of surfactants has to be above 15 % by weight in order to achieve a microemulsion according to the definition above.

None of the prior art documents discloses a non-toxic microemulsion suitable for parenteral administration of substances having a low solubility in water, which microemulsion could be either in form of a oil-in-water microemulsion or a bicontinuous microemulsion and also is easy to prepare. Thus, there is a need for a new vehicle having the above listed characteristics.

Brief description of the invention

The object of the present invention is to provide a pharmaceutically acceptable non-toxic vehicle which increases the solubility of compounds having a low solubility in water, and which vehicle is in form of a microemulsion which is stable, translucent and suitable for parenteral as well as oral and transdermal administration of one or more active compounds.

The microemulsion is defined in claim 1 and further preferred embodiments of the invention are disclosed in claims 2-18.

Detailed description of the invention

According to the present invention a microemulsion which is suitable for parenteral as well as oral and transdermal administration of one or more active compounds is disclosed. It has surprisingly been found that by using at least two types of modifiers it is possible to minimize the amount of the surfactant and thus, also the toxicity is minimized.

The present microemulsion comprises

- a polar phase containing water and optionally an agent for obtaining isotonic conditions, and one or more components (modifiers) for adjusting the polarity,
- a surfactant film modifier,
- a non-polar phase consisting of at least one pharmaceutically acceptable oil and
- a mixture of a hydrophilic and a hydrophobic surfactant up to 15% by weight of the total microemulsion, preferably 4-12%.

The polar phase includes water and optionally an agent for obtaining isotonic conditions, e.g a NaCl- or glycerol solution. The polar phase also includes compound/compounds which decrease the polarity of the polar phase and thus, lowering the amount of surfactant. These compounds are called modifiers. Examples of modifiers are; polyethylene glycol 400 (PEG 400), polyethylene glycol 300 (PEG 300), polyethylene glycol 200 (PEG 200); propylene glycol; glucofurool (polyethyleneglycol tetrahydrofurfurylether); glycerol; sorbitol; mannitol; monosaccharides; disaccharides; dimethyl acetamide; solketal;

methypyrrolidone; 1-hydroxyethyl-2-pyrrolidon or hydroxyethyl lactamide. Preferred modifiers are one or more of the following; polyethylene glycol 400 (PEG 400), polyethylene glycol 300 (PEG 300), polyethylene glycol 200 (PEG 200); propylene glycol; glucofurol; glycerol; sorbitol; mannitol; monosaccharides or disaccarides. More preferred modifiers are one or more of the following; polyethylene glycol 400 (PEG 400), polyethylene glycol 300 (PEG 300), polyethylene glycol 200 (PEG 200); propylene glycol; glucofurol and glycerol. Most preferred modifier is the compound PEG 400.

The surfactant film modifier will be partially incorporated in the polar part of the surfactant film, thereby both increasing the area per lipid polar head group, and thus changing the spontaneous curvature of the lipid layers from being slightly curved toward water to become more planar or curved toward oil, and decreasing the stability of the lamellar liquid crystalline phase. Preferably the surfactant film modifier is ethanol, but also C₃-alcohols might be useful in case of transdermal administration.

The non-polar phase consists of at least one pharmaceutically acceptable oil which may be a triglyceride containing fatty acids having 4-18 carbon atoms; a diester of propylene glycol containing fatty acids having 4-18 carbon atoms; a monoester of a fatty acid containing an alcoholic part consisting of 1-5 carbon atoms and a fatty acid part having 8-22 carbon atoms or mixtures thereof.

Preferably the non-polar phase consists of a triglyceride containing at least 70 % of fatty acids having 8-10 carbon atoms; a diester of propylene glycol containing at least 70 % of fatty acids having 8-10 carbon atoms; or of a monoester of a fatty acid such as isopropylmyristate, isopropylpalmitate or ethyloleate or mixtures thereof. More preferred the non-polar phase consists of a triglyceride containing at least 70 % of fatty acids having 8-10 carbon atoms; a diester of propylene glycol containing at least 70 % of fatty acids having 8-10 carbon atoms or of isopropylmyristate. Most preferred the non-polar phase consists of either a triglyceride containing at least 70 % of fatty acids having 8-10 carbon atoms or isopropylmyristate.

The hydrophobic surfactant is one of lecithin, sphingolipids and galacto lipids. Most preferred hydrofobic surfactant is purified soybean lecithin, comprising at least 90 % phosphatidyl cholin. The non-ionic hydrophilic surfactant could be ethoxylated castor oil; 5 ethoxylated fatty esters; sucrose fatty esters; mono-, di- and triesters of sorbitol and sorbitan and polyoxyethylene derivatives thereof; alkyl glucosides or alkyl polyglucosides; ethoxylated mono-hydroxy stearic acid and bile salts. Preferably the hydrophilic surfactant is polyethylene glycol (15)-12-hydroxy stearate, an alkylmaltoside, bile salts or mixtures thereof.

10 The present invention provides both an oil-in-water microemulsion and a bicontinuous emulsion. By changing the ratio between the polar and the non-polar phase and also the amount of the modifiers mixed with the water in the polar phase, it is possible to obtain a microemulsion either in an oil-in-water type or bicontinuous type. The microemulsion 15 according to present invention may be used for solubilizing active compounds for intravenous, intraperitoneal or intraarterial administration. It may also be used for preparations of active compounds having a low solubility in water for subcutaneous, intramuscular or transdermal administration. A further use of the microemulsion could be solubilization and increased absorption of active compounds having a low solubility in 20 water when administered orally.

The active compound could e.g. be a proton pump inhibitor, calcium channel blocker, beta blocker, anesthetic, steroid, antioxidant, renin inhibitor, alkaloid, cytostatica, anti-coagulant, lipid regulating agent, anti-depressant, neuroleptic, immunosuppressant, 25 immunomodulator, antibiotic, anti-inflammatory agent.

Preparation

The microemulsion could be prepared by mixing the components together in no particular order and allow the mixture to equilibrate typically two or three days. The equilibrating procedure could be shortened by gentle heating of the mixture to about 40°C, and stirring or shaking the mixture at regular intervals. It should be noted that the optimum concentration of the modifiers may have to be optimized for different batches of soybean lecithin and also for different active compounds.

The invention is illustrated more in detail by the following examples.

Example 1

The following components were mixed together in a glass vial:

1a

Component	Composition	Amount (g)	wt%
Surfactants	Epicuron 200 ¹	0.28	7.0
	Soluthol HS15 ²	0.196	4.9
Aq-phase	water	1.11	27.8
	PEG 400 ³	0.456	11.4
	ethanol (99.5%)	0.196	4.9
oil phase	Miglyol 810 ⁴	1.76	44.0

1b

Component	Composition	Amount (g)	wt%
Surfactants	Epicuron 200 ¹	0.7	7.0
	Soluthol HS15 ²	0.49	4.9

Component	Composition	Amount (g)	wt%
Aq-phase	water	1.66	16.6
	PEG 400 ³	0.685	6.85
	ethanol (99.5%)	0.293	2.93
oil phase	Miglyol 810 ⁴	6.17	61.7

1c

Component	Composition	Amount (g)	wt%
Surfactants	Epicuron 200 ¹	0.28	7.0
	Soluthol HS15 ²	0.196	4.9
Aq-phase	0.9 % NaCl	1.11	27.8
	PEG 400 ³	0.456	11.4
	ethanol (99.5%)	0.196	4.9
oil phase	Miglyol 810 ⁴	1.76	44.0

1d

Component	Composition	Amount (g)	wt%
Surfactants	Epicuron 200 ¹	0.70	7.0
	Soluthol HS15 ²	0.49	4.9
Aq-phase	0.9 % NaCl	1.66	16.6
	PEG 400 ³	0.685	6.85

Component	Composition	Amount (g)	wt%
	ethanol (99.5%)	0.293	2.93
oil phase	Miglyol 810 ⁴	6.17	61.7

¹Epicuron 200 is a purified soybean lecithin manufactured by Lucas Meyer, Germany.

²Solutol HS15 is a polyoxyethylene glycol(15)-12-hydroxy stearat manufactured by
5 BASF, Germany.

³PEG 400 is polyethylene glycol with the average molecular weight of 400 g/mole.

⁴Miglyol 810 is a triglyceride with the chainlength distribution of the fatty acids according
10 to the manufacturer: C_{6:0} = 2% max, C_{8:0} = 70-80%, C_{10:0} = 18-28%, C_{12:0} = 2% max.

The glass vial was sealed and the mixture was shaken using a vortex mixer for a given number of minutes and then kept in a water bath keeping a constant temperature of 37°C for two days. The vial was shaken using the vortex mixer two or three times a day. After
15 two days the mixture appeared as a transparent slightly viscous one phase liquid. The mixture was kept at 25°C for one week and showed no sign of phase separation. The sample was tested by visual appearance and using cross polarized filters to detect any sign of liquid crystalline phases. The temperature was raised to 37°C and the sample was inspected after two days using the same procedure without any sign of phase separation.
20 The sample was then kept in room temperature and inspected at regular intervals and the stability was at least six months.

Example 2

25 The following components were mixed together in a glass vial:

10

2a:

Component	Composition	Amount (g)	wt%
Surfactants	Epicuron 200	0.120	3.0
	Solutol HS15	0.240	6.0
Aq-phase	water	1.274	31.8
	PEG 400	0.385	9.6
	ethanol	0.165	4.1
Oil phase	isopropylmyristate	1.828	45.6

2b:

Component	Composition	Amount (g)	wt%
Surfactants	Epicuron 200	2.8	2.8
	dodecylmaltocid	1.2	1.2
Aq-phase	water	38.17	38.17
	glucose	9.58	9.58
	ethanol	10.08	10.08
Oil phase	isopropylmyristate	38.17	38.17

5

2c:

Component	Composition	Amount (g)	wt%
Surfactants	Epicuron 200	4.9	4.9
	dodecylmaltocid	2.1	2.1

11

Component	Composition	Amount (g)	wt%
Aq-phase	water	35	35
	glucose	10	10
	ethanol	13	13
Oil phase	isopropylmyristate	35	35

2d:

Component	Composition	Amount (g)	wt%
Surfactants	Epicuron 200	6.5	6.5
	Na-taurocholate	1.0	1.0
Aq-phase	water	39.25	39.25
	PEG 400	7.0	7.0
	ethanol	7.0	7.0
Oil phase	isopropylmyristate	39.25	39.25

5

2e:

Component	Composition	Amount (g)	wt%
Surfactants	Epicuron 200	6.5	6.5
	Na-taurocholate	1.0	1.0
Aq-phase	water	38.75	38.75

Component	Composition	Amount (g)	wt%
	ethanol	7.0	7.0
Oil phase	isopropylmyristate	39.25	39.25

The mixture was equilibrated according to the process in example 1, and after two days the mixture appeared as a transparent slightly viscous one phase liquid. The mixture was kept at 25°C for one week and showed no sign of phase separation. The sample was tested by visual apperance and using cross polarized filters to detect any sign of liquid crystalline phases. The temperature was raised to 37°C and the sample was inspected after two days using the same procedure without any sign of phase separation.

Example 3

A microemulsion according to example 1 was prepared and the solubility of two sparingly soluble substances, felodipine (ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate) and cis-4b,5,9b,10-tetrahydro-4b,7,9,9b-tetramethyl-8-ethoxy-indeno(1,2-b)indole, hereinafter called the indeno indole, were tested. Different amounts of the substances were added to 1 ml samples of the microemulsion placed in glass vials. The samples were rotated for 48 hours to allow a complete wetting of the solid substance. The samples were than kept in a waterbath at 25°C for at least one week before inspection. The samples were inspected for any solid substance or phase separation and the maximum solubility was defined as the range between the last sample in each serie without any trace of solids or phase separation, and the first sample with remaining and undissolved substance or a phase separation.

Table 1. Solubility of felodipine and the indeno indole in a microemulsion prepared according to example 1.

	Sol. in water mg/l	sol. in microemulsion 1a mg/l	sol. in microemulsion 1b mg/l
Felodipine	0.8	5000-10000	10 000-15 000
The indeno indole	2.0	40 000-50 000	60 000-75 000

Example 4

The effect of a microemulsion according to example 1a on different pharmacological parameters in conscious rats was compared with a 50 % PEG 400/water solution using saline as a control.

Biological effect

Experimental procedure and material

Animals

Adult, male Sprague-Dawley rats from Denmark, were used. After arrival at Astra Hässle AB, the animals were allowed at least one week to acclimatise before surgery. They were maintained in standard rat cages with aspen-chip bedding in a room with regulated temperature (20 - 22 °C), humidity (50 - 70 %) and with a 12/12 h light/dark cycle. The animals had free access to pellets and to tap-water from bottles.

Surgery

The day before the experiments, the animals were anaesthetised with Methohexital Sodium (Brietal, Lilly, Indianapolis, Ind, USA) 60 mg/kg i.p. and catheters were inserted in the right jugular vein (PE 25 for i.v. drug injections) and the tail artery (8 cm long PE 10 connected to PE 90 for blood pressure recordings). The tip of the arterial catheter was placed in the abdominal aorta below the renal arteries. ECG electrodes were placed under the skin over the apex and the right shoulder, and the ground electrodes were placed over the lumbar spine. This corresponds to a CR-recording. After the surgical

procedure the animal was placed alone in a cage in a room with regulated humidity, temperature and light/dark cycle. The rats were also connected to a swivel system (Carnegie, Stockholm, Sweden), which delivered 1.0 ml sterile saline per hour via the arterial pressure line.

5

Hemodynamic and ECG recordings:

The day after the acute surgical procedure, the experiments were performed with the conscious rat residing in its own cage. The tail artery catheter was connected via a swivel
10 allowing the animal to move relatively freely. The arterial pressure catheter was connected to a pressure transducer. The catheter was kept patent by slow infusion of 1.0 ml NaCl/h via a side tube of the arterial pressure line. The side tube was a 60 cm long PE 10 catheter, which has a high internal resistance. Thus, the side tube does not damp out arterial pulsations. Heart rate (HR) was measured from the undamped arterial pressure
15 signal with a rate meter, and mean arterial pressure (MAP) was obtained by electronic filtering. The parameters from 4 animals were displayed simultaneously on a Grass polygraph (model 7 D). The ECG electrodes were connected intermittently to a Grass (7P6) ECG pre-amplifier. The ECG was recorded on a calibrated Siemens Elema Inkjet recorder.

20

The mean arterial pressure and heart rate signals were fed into a Datatranslation (DT 2801) AD converter placed in a Compaq 386SX computer. The computer program PC-LAB (written by Jan Axenborg and Ika Hirsch, AB Astra Hässle) sampled values of arterial pressure and heart rate repeatedly during the course of the experiments. The
25 program sampled arterial pressure and heart rate for 20 s and calculated the average values of each 20 s period once every minute during the 4.5 h of experiments (i.e. created a file with 285 values of the individual parameters from 3-4 rats simultaneously).

In addition, the PC-LAB program sampled the ECG from all 4 rats 8 times during the
30 course of the experiment (see Fig. 1). ECG signals were sampled at 800 Hz for 4 s, i.e.

about 20 ECG cycles from each rat were stored in the computer memory. This array of samples from 4 rats was then transferred to a VAX-computer at AB Astra Hässle and was analysed with the PC-LAB program (written by Jan Axenborg). The PC-LAB program calculated an average ECG from about 20 cycles. The 2nd cycle is the triggering cycle and is used for all calculations. From the average ECG, we calculated the PQ-time and QRS-duration in milliseconds.

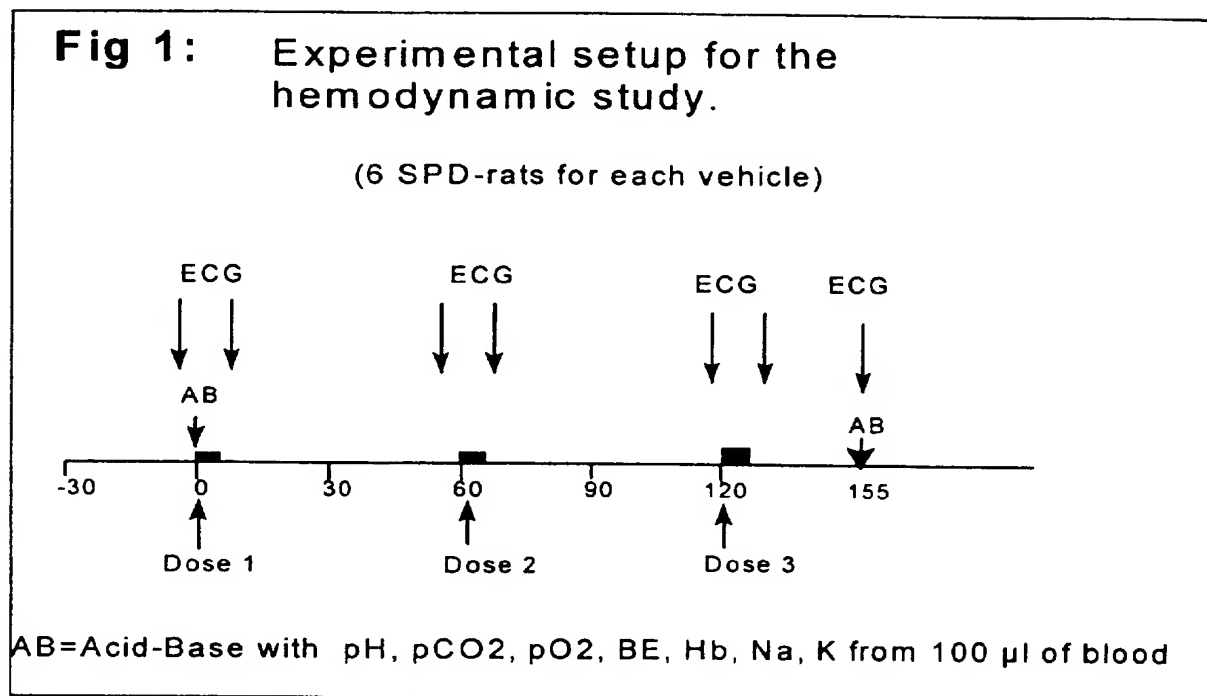
Experimental procedures

The experimental procedure is illustrated in Fig. 1. The experiment was performed on 3 different vehicles.

The basic hemodynamic parameters were recorded for 30 min. (see Fig. 1). Then the animals received 3 infusions of the vehicle given during 5 min. The volume was 0.3, 1 and 3 ml/kg for saline and PEG 400 and 0.15, 0.5 and 1.5 ml/kg for the microemulsion. The infusions were given 60 min. apart.

Blood samples for acid-base balance and blood gas determinations were obtained twice (before the first dose and at the end of the experiment).

ECG was obtained at intervals shown in Fig 1.



5 CALCULATIONS AND STATISTICS

Arterial blood pressure and heart rate data

The data for each animal (n=6 for all experiment except heart rate data for PEG 400 (50%) where n=5) were normalized using the mean of the first three data points as a baseline and the deviation from this baseline for each datapoint was calculated. The two vehicles were compared by calculating the mean difference between each vehicle (PEG 400 (50%) or microemulsion) and the control (saline). A 95% confidence interval using the pooled variances and the t-distribution compensated for consecutive measurements with the Bonferoni technique for the data points immediately after each infusion was calculated.

ECG, acid-base balance, blood gases and plasma electrolytes

The results are presented as mean values and the variability is expressed as SEM (n=6).

RESULTS AND CONCLUSIONS

A microemulsion according to example 1a was compared with a 50% aqueous solution of PEG 400 which is a co-solvent often used for intravenous administration. Saline was used as a control. The results are shown in tables 1 - 3. The data shows that it is possible to administrate, by intravenous infusion to conscious rats, a microemulsion according to example 1a up to 0.5 ml/kg without causing any significant effect on acid-base balance, blood gases, plasma electrolytes, heart rate or PQ time. There is a significant but very small decrease in the arterial blood pressure immediately after the second dose but this is considered to be of no biological relevance.

At the highest dose, 1.5 ml/kg (microemulsion) and 3.0 ml/kg (PEG 400 (50%)), the effect of the microemulsion and PEG 400 solution was very similar. A small increase in arterial blood pressure, for the microemulsion only, and a moderate bradycardic effect together with a temporary prolongation of the PQ time for both vehicles.

The solubility of felodipine and the indenoindol used in example 3 in PEG 400 (50%) are 0.7 mg/ml and 0.2 mg/ml respectively. Using the microemulsion it is thus possible to administrate 5 times more of felodipine and over 100 times more of the indenoindol compared to a 50% solution PEG 400. The microemulsion is surprisingly superior compared to The PEG 400 solution for solubilization and administration of compounds with a low solubility in water.

Table 1a. Arterial blood pressure (mm Hg)

Time(min)	-25.5	-15.5	-5.5	4.5	14.5	24.5	34.5	44.5	54.5	64.5	74.5	84.5	94.5	104.5	114.5	124.5	134.5	144.5
Peg 400-sal	-0.4	1.9	-2.7	0.8	1.2	4.7	2.2	-1.8	0.4	3.6	5.9	5.9	2.9	2.4	0.8	5.5	0.3	0.7
Conf. int.(95%)				+6.0						+10.4						+10.6		
Microem.-sal	2.8	-1.2	-1.4	2.5	-1.7	5.3	6.2	-0.7	-0.3	6.6	3.6	4.5	4.3	1.4	4.1	13.0	3.5	8.9
Conf. int (95%)				+5.3						+8.6						+8.7		

Table 1b. heart rate (beats/min)

Time(min)	-25.5	-15.5	-5.5	4.5	14.5	24.5	34.5	44.5	54.5	64.5	74.5	84.5	94.5	104.5	114.5	124.5	134.5	144.5
Peg 400-sal	0.2	13.7	3.2	-15.2	-2.5	11.3	2.7	-5.5	4.6	-20.3	4.3	-1.9	1.6	4.5	0.6	-43.7	-26.9	0.3
Conf. int.(95%)				+8.7						+20.4						+15.4		
Microem.-sal	8.0	7.0	6.9	-12.3	-10.1	21.9	20.9	-5.0	4.8	-24.7	-13.3	7.1	19.9	16.7	18.5	-36.9	-16.1	18.8
Conf. int (95%)				+13.9						+23.0						+20.4		

Table 2. PQ-time (msec)

Time(mln):	29	36	59	66	119	126	155
Saline:	45.8	43.7	45.3	45.5	46.0	45.1	47.0
SEM:	0.99	0.86	0.86	0.68	1.02	0.40	0.95
PEG 400 (50%):	45.3	45.3	44.7	46	44.2	51	46.3
	1.42	1.48	1.57	1.51	1.37	2.11	1.71
Microemulsion:	46.2	47.3	46.5	49	44.5	51	44.5
SEM:	1	0.68	1.04	0.98	1.1	1.77	0.81

Table 3. Acid-base balance, blood gases and plasma electrolytes.

	pH	pCO ₂ (kPa)	pO ₂ (kPa)	BE (mmol/L)	Na (mmol/L)	K (mmol/L)						
Time (min):	0	155	0	155	0	155						
Saline	7.49	7.49	4.45	4.93	12.13	12.08	2.73	4.42	142.83	140.67	3.47	3.73
SEM	0.01	0.01	0.18	0.20	0.12	0.25	0.62	1.10	0.75	0.21	0.40	0.14
PEG 400 (50%)	7.47	7.47	4.37	4.39	11.93	12.06	0.83	0.85	143.67	142.83	3.00	3.07
SEM	0.01	0.01	0.09	0.10	0.24	0.35	0.59	0.56	0.88	0.70	0.14	0.15
Microemulsion	7.47	7.47	4.91	4.24	11.48	11.13	3.12	0.58	141.50	143.33	3.32	2.93
SEM	0.01	0.01	0.23	0.18	0.62	0.73	1.09	0.57	1.18	0.80	0.27	0.13

Claims

1. A non-toxic oil-in-water or bicontinuous microemulsion as a vehicle for administration
5 of one or more active compounds having a low solubility in water, which microemulsion contains
- a polar phase containing water and optionally an agent for obtaining isotonic conditions, and one or more components (modifiers) for adjusting the polarity of the polar phase,
 - a surfactant film modifier,
 - 10 - a non-polar phase consisting of at least one pharmaceutically acceptable oil and
 - a mixture of a hydrophilic surfactant and a hydrophobic surfactant up to 15% by weight of the total microemulsion, wherein the hydrophobic surfactant is chosen from a group consisting of lecithin, sphingolipids or galacto lipids.
- 15 2. A microemulsion according to claim 1 c h a r a c t e r i z e d in that the component for adjusting the polarity of the polar phase is one or more of
- a) polyethylene glycol, i.e. polyethylene glycol 200, polyethylene glycol 300 or polyethylene glycol 400; propylene glycol; glucofurool; glycerol; or one or more of
 - b) sorbitol; mannitol; monosaccharides; disaccarides; or one or more of
 - 20 c) dimethyl acetamide; solketal; methylpyrrolidone; 1-hydroxyethyl-2-pyrrolidon or hydroxyethyl lactamide.
3. A microemulsion according to claim 2 c h a r a c t e r i z e d in that the component for adjusting the polarity of the polar phase is one or more of
- 25 a) polyethylene glycol; propylene glycol; glucofurool; glycerol; or one or more of
 - b) sorbitol; mannitol; monosaccharides or disaccarides.
4. A microemulsion according to claim 2 and 3 c h a r a c t e r i z e d in that the component for adjusting the polarity of the polar phase is polyethylene glycol 400.

5. A microemulsion according to claim 1 characterized in that the agent for obtaining isotonic conditions is a solution of NaCl or glycerol.

6. A microemulsion according to claim 1 characterized in that the surfactant film modifier is an alcohol with 2-3 carbon atoms.

7. A microemulsion according to claim 6 characterized in that the surfactant film modifier is ethanol.

8. A microemulsion according to claim 1 characterized in that the pharmaceutically acceptable oil in the non-polar phase is a triglyceride containing 4-18 carbon atoms; a diester of propylene glycol containing fatty acids having 4-18 carbon atoms; a monoester of fatty acid containing an alcoholic part consisting of 1-5 carbon atoms or a fatty acid part having 8-22 carbon atoms, or mixtures thereof.

9. A microemulsion according to claim 8 characterized in that the pharmaceutically acceptable oil in the non-polar phase is a triglyceride containing at least 70 % of fatty acids having 8-10 carbon atoms; a diester of propylene glycol containing at least 70 % of fatty acids having 8-10 carbon atoms; a monoester such as isopropylmyristate, isopropylpalmitate, ethyloleate or mixtures thereof.

10. A microemulsion according to claim 9 characterized in that the pharmaceutically acceptable oil in the non-polar phase is a triglyceride containing at least 70% of fatty acids having 8-10 carbon atoms; isopropylmyristate or mixture thereof.

11. A microemulsion according to claim 1 characterized in that the hydrophobic surfactant is purified soybean lecitin comprising at least 90 % phosphatidyl cholin.

12. A microemulsion according to claim 1 characterized in that the hydrophilic surfactant is ethoxylated castor oil; ethoxylated fatty esters; sucrose fatty esters; mono-, di-,

and triesters of sorbitol or sorbitan and polyethylene derivatives thereof; alkyl glucosides or alkyl polyglucosides; ethoxylated mono-hydroxy steric acid; bile salts or mixtures thereof.

5 13. A microemulsion according to claim 12 characterized in that the hydrophilic surfactant is polyethylene glycol(15)-12-hydroxy stearate, alkylmaltoside, bile salts or mixtures thereof.

10 14. A microemulsion according to claim 1 characterized in that the amount of surfactant is up to 15 % by weight of the total microemulsion.

15 15. A microemulsion according to claim 1 characterized in that the amount of surfactant is 4-12 % by weight of the total microemulsion.

16. A microemulsion according to claim 1 characterized in that it is an oil-in-water microemulsion.

17. A microemulsion according to claim 1 characterized in that the active compound is a pharmaceutical.

20

18. A microemulsion according to claim 17 characterized in that the active compound is a proton pump inhibitor, calcium channel blocker, beta blocker, anesthetics, steroid, antioxidant, renin inhibitor, alkaloid, cytostatica, antocoagulant, lipid regulating agent, antidepressant, neuroleptic, immunosuppressant, immunomodulator, antibiotic or an
25 antiinflammatory agent.

19. A process for the preparation of a microemulsion according to claim 1
characterized in mixing the components together in no particular order and allow
30 the mixture to equilibrate typically one or two days, whereby the equilibrating procedure

could be shortened by gentle heating of the mixture, about 40°C, and stirring or shaking the mixture at regular intervals.

- 5 20. Use of a microemulsion according to any one of claims 1 - 18 for administering an effective amount of one or more active compounds to a host in need of such active compounds.
- 10 21. Use of a microemulsion according to claim 20 for parenteral administration of an effective amount of one or more active compounds to a host in need of such active compounds.
22. Use of a microemulsion according to claim 20 for oral administration of an effective amount of one or more active compounds to a host in need of such active compounds.
- 15 23. Use of a microemulsion according to claim 20 for transdermal administration of an effective amount of one or more active compounds to a host in need of such active compounds.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/01097

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/107

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EDOC, PAJ, PCI, USPATFULL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0334777 A1 (GATTEFOSSE S.A.), 27 Sept 1989 (27.09.89), column 2, line 56 - column 3, line 39, claim --	1-23
X	EP 0391369 A2 (YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM), 10 October 1990 (10.10.90), see claims --	1-23
A	EP 0651994 A1 (DIETL, HANS, DR.), 10 May 1995 (10.05.95) -----	1-23

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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Date of the actual completion of the international search

27 November 1996

Date of mailing of the international search report

29 - 11 - 1996

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INTERNATIONAL SEARCH REPORT

Information on patent family members

28/10/96

International application No.

PCT/SE 96/01097

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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EP-A2- 0391369	10/10/90	AT-T- 110563 AU-B- 614465 AU-A- 5292790 CA-A, C- 2013755 DE-D, T- 69011922 JP-A- 2290809 JP-B- 7121857 US-A- 5364632 IL-A- 93558	15/09/94 29/08/91 11/10/90 05/10/90 12/01/95 30/11/90 25/12/95 15/11/94 27/11/95
EP-A1- 0651994	10/05/95	DE-A- 4338046	11/05/95



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : A61K 9/107</p>	<p>A1</p>	<p>(11) International Publication Number: WO 97/09964 (43) International Publication Date: 20 March 1997 (20.03.97)</p>
<p>(21) International Application Number: PCT/SE96/01097 (22) International Filing Date: 4 September 1996 (04.09.96) (30) Priority Data: 9503143-1 12 September 1995 (12.09.95) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventor; and (75) Inventor/Applicant (for US only): VON CORSWANT, Chris- tian [SE/SE]; Ringleken 14, S-431 69 Mölndal (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With a revised version of the international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> <p>(88) Date of publication of the revised version of the international search report: 30 October 1997 (30.10.97)</p>
<p>(54) Title: MICROEMULSIONS FOR USE AS VEHICLES FOR ADMINISTRATION OF ACTIVE COMPOUNDS</p> <p>(57) Abstract</p> <p>A non-toxic oil-in-water or bicontinuous microemulsion as a vehicle for administration of one or more active compounds having a low solubility in water, which microemulsion contains: a polar phase containing water and optionally an agent for obtaining isotonic conditions, and one or more components (modifiers) for adjusting the polarity of the polar phase; a surfactant film modifier; a non-polar phase consisting of at least one pharmaceutically acceptable oil; and a mixture of a hydrophilic surfactant and a hydrophobic surfactant up to 15 % by weight of the total microemulsion, wherein the hydrophobic surfactant is chosen from a group consisting of lecithin, sphingolipids or galacto lipids.</p>		

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GA	Gabon			VN	Viet Nam

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/01097

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IPC6: A61K 9/107
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	EP 0728460 A1 (L'OREAL), 28 August 1996 (28.08.96) --	1-23
X	EP 0391369 A2 (YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM), 10 October 1990 (10.10.90), see claims --	1-23
A	EP 0651994 A1 (DIETL, HANS, DR.), 10 May 1995 (10.05.95) -- -----	1-23

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 9 Sept 1997	Date of mailing of the international search report 17 -09- 1997
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Patrick Andersson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

Information on patent family members

06/08/97

International application No.

PCT/SE 96/01097

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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EP 0651994 A1	10/05/95	DE 4338046 A	11/05/95



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/46, 31/44	A1	(11) International Publication Number: WO 97/25030 (43) International Publication Date: 17 July 1997 (17.07.97)
(21) International Application Number: PCT/SE96/01738 (22) International Filing Date: 20 December 1996 (20.12.96) (30) Priority Data: 9600073-2 8 January 1996 (08.01.96) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventor; and (75) Inventor/Applicant (for US only): LUNDBERG, Per, Johan [SE/SE]; Torsgatan 6, S-431 38 Mölndal (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: MULTIPLE UNIT EFFERVESCENT DOSAGE FORMS COMPRISING PROTONPUMP INHIBITOR		
(57) Abstract A new tableted multiple unit effervescent dosage form containing an acid susceptible proton pump inhibitor in the form of the racemate, an alkaline salt thereof or one of its single enantiomers or an alkaline salt thereof, and effervescent tablet constituents. The proton pump inhibitor is preferably omeprazole or an alkaline salt thereof, or S-omeprazole or an alkaline salt thereof. Further the invention refers to a method for the manufacture of such a formulation, and the use of such a formulation in medicine.		

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Multiple unit effervescent dosage forms comprising
protonpump inhibitor.

Field of the invention.

5 The present invention is related to new pharmaceutical preparations in the form of a
tableted multiple unit effervescent dosage form comprising an active substance in the form
of an acid susceptible proton pump inhibitor, i.e. acid labile H^+K^+ ATPase inhibitors. The
novel tableted dosage form is intended for oral use. Furthermore, the present invention
refers to a method for the manufacture of such preparations and, to the use of such
10 preparations in medicine.

Background of the invention

15 Acid labile H^+K^+ ATPase inhibitors also named as proton pump inhibitors are for instance
compounds known under the generic names omeprazole, lansoprazole, pantoprazole,
pariprazole, leminoprazole and others.

These active substances are useful for inhibiting gastric acid secretion in mammals and
20 especially in man. In a more general sense, they may be used for prevention and treatment
of gastric-acid related diseases in mammals and especially in man, including e.g. reflux
oesophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, they may
be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect
is desirable e.g. in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, in
25 patients with symptomatic gastro oesophageal reflux disease, and in patients with
gastrinomas. They may also be used in patients in intensive care situations, in patients with
acute upper gastrointestinal bleeding, pre-and postoperatively to prevent aspiration of
gastric acid and to prevent and treat stress ulceration. Further, they may be useful in the
treatment of psoriasis as well as in the treatment of Helicobacter infections and diseases
30 related to these.

The active compounds are, however, susceptible to degradation/transformation in acidic reacting and neutral media. The degradation is catalyzed by acidic reacting compounds. The active compounds are stabilized with alkaline reacting compounds. Thus, the active substance being a proton pump inhibitor is best protected by an enteric coating layer. There are different enteric coating layered preparations of omeprazole as well as other proton pump inhibitors described in the prior art, see for example US-A 4,786,505 (AB Hässle).

There has been a demand for a formulation with a rapid dissolution and a quick onset of action, furthermore a formulation which is pleasant to take for the patient and also which is suitable for patients with swallowing difficulties (dysphagia). There are a number of dosage forms that hold a good deal of promise in administering proton pump inhibitors. However, it has been difficult to find a vehicle which can satisfy all of many and some times conflicting needs and desires for such a dosage form.

One possible vehicle for administration of these active agents is effervescent tablets.

Effervescence provides generally some measure of taste-masking. Prior to being taken by the patient, an effervescent composition is dissolved and/or dispersed in for example an aqueous medium, such as drinking water. Dissolution and/or dispersion takes place rapidly, with effervescence to give an agreeable presentation of the drug, particularly for patients who do not like tablets or find difficulty in swallowing tablets.

Effervescent compositions usually contain, in addition to the active ingredient, a source of carbon dioxide (such as an alkaline carbonate or bicarbonate) and an acid (such as for instance citric acid). The use of an acid in effervescent compositions in which the active ingredient is an acid labile substance such as an acid susceptible proton pump inhibitor presents a problem due to the instability of the proton pump inhibitor in the presence of acid.

Replacement of citric acid by monosodium citrate still fails to give a satisfactory level of stability of an acid labile histamine H₂ -antagonist, whilst replacement of citric acid by disodium citrate results in insufficient effervescence and a prolonged dissolution time. EP 233853 proposes a mixture of monosodium citrate and disodium citrate as a solution to the problem. GB 2 219 940 A, proposes replacement of citric acid or the mixture of citrates proposed in EP 233853 by a monoalkalimetal citrate (monosodium citrate).

Effervescent tablets containing acid-sensitive agents have been manufactured by coating the acidic particles in the acid-base couple with a coating of a base to separate the pharmaceutically active substance, i.e. the acid-sensitive agent, from the acid of the effervescence, see for instance WO 94 21,239. The proposed solution results in that the active drug comes into contact with the resulting buffer when dissolving the tablet. Thus, the active drug must be stable in that buffer at the given pH. Furthermore, if the active drug has a bad taste, there will be problems to mask it. (For instance, omeprazole is such a compound that has a strongly bitter taste).

Another way to make effervescent tablets containing acid-labile drugs, such as erythromycine, has been proposed as described in US 4,289,751. The active substance is incorporated in the effervescent tablet, in intimate contact with the effervescing acid-base couple. The effervescent tablet is then coated with an enteric coating polymer. The aim of the preparation is that the tablet will be protected from the strongly acidic environment in the stomach by the enteric coating layer during the passage thereof. In the small intestines, the enteric coating layer is dissolved and the effervescent effect takes place in the intestines. One drawback with such a dosage form is that patients can experience problems due to the carbon dioxide liberated inside the gastrointestinal channel. Another drawback is varying residence time in the stomach before the tablet can arrive to an environment where the active substance can be dissolved, absorbed and can exert its effect.

Korean pat. appl. No. 93-17902 proposes another composition comprising an enteric coated tablet with an effervescent mixture layer inside the enteric coating. Also Korean pat.

appl. No. 94-3190 describes a formulation of omeprazole with an effervescent mixture inside the enteric coating.

A way to circumvent the problems associated with the composition proposed in US 4,289,751, i.e. with carbon dioxide created inside the gastrointestinal channel etc., and to avoid direct contact between the pharmaceutically active substance, i.e. the acid-labile compound, and acidic substances of the effervescence, and further to avoid direct contact of the active substance with a solution buffered to unsuitable pH, would be to use the active substance in the form of small enteric coating layered units comprising the pharmaceutically active substance. Such units are coating layered with a polymeric layer not dissolving in the solution formed when the effervescent tablet is dissolved. These small coating layered units are taste-masked as they maintain their coating layer intact during and after intake of the effervescent dispersion and during passage of the stomach. The coating layer starts to dissolve upon arrival at the appropriate place in the gastrointestinal channel, i.e. in the small intestines (duodenum). The present invention now surprisingly provides such enteric coating layered units suitable for an effervescent formulation.

Preparation of a multiple unit tableted dosage form arises specific problems when enteric coating layered pellets containing acid susceptible proton pump inhibitors as active substances are compressed into tablets. If the enteric coating layer does not withstand the compression of the pellets into a tablet the susceptible active substance will be destroyed both by the acidic solution/dispersion formed upon effervescence or by penetrating acidic gastric juice upon administration, i.e. the acid resistance of the enteric coating layer of the pellets will not be sufficient in the tablet after compression.

Summary of the invention

The Applicant has now surprisingly found that effervescent tablets according to the present invention comprising enteric coated units of an acidic susceptible proton pump inhibitor can be manufactured by compressing said units into tablets without significantly affecting the

properties of the enteric coating. As explained above, if the enteric coating is damaged during compression of the enteric coated units the acid resistance of said enteric coating in the manufactured tablets will not be sufficient and the manufactured tablets will not fulfil standard requirements on enteric coated articles, such as those defined in the United States Pharmacopeia USP. Furthermore, the active substance may be destroyed by the acidic solution/dispersion obtained by the effervescence, if such requirements not are fulfilled.

One object of the present invention is to provide a tableted multiple unit effervescent dosage form comprising an acid susceptible proton pump inhibitor, or an alkaline salt thereof or one of its single enantiomers or an alkaline salt thereof, in which the active substance is in the form of enteric coating layered units compressed together with effervescent tablet excipients into such an effervescent tablet. The enteric coating layer(s) covering the individual units of active substance has properties such that the compression of the units into a tablet does not significantly affect the acid resistance of the enteric coated units. The active substance is prevented from degradation and dissolution in acidic media and the dosage form has a good stability during long-term storage. The enteric coating covering the individual units disintegrates/dissolves rapidly in near neutral or alkaline media.

The tableted multiple unit effervescent dosage form is especially suitable for patients with swallowing disorders and in pediatrics.

Detailed description of the invention.

The novel tableted multiple unit effervescent dosage form comprising an active substance in the form of an acid susceptible proton pump inhibitor, or an alkaline salt thereof or one of its single enantiomers, or an alkaline salt thereof is characterized in the following way.

An effervescent tablet is compressed from a mixture of enteric coated layered pellets comprising the active substance and effervescent tablet constituents, and optionally other tablet excipients. Dissolution of the tablet in water gives such a pH value that the enteric

coating layer of the pellets will not dissolve, i.e. a pH value normally less than 5.5, but depending on the specific enteric coating material used. Furthermore, the formulation is characterized in that the tablet *per se* is rapidly dissolving, and that it may contain taste improving agents, colourants, technical additives such as lubricating agents, disintegrants and wetting agents, and other tablet excipients.

The enteric coating layered units containing active substance and optionally alkaline reacting substances, are mixed with effervescent tablet constituents and optionally other excipients. The mixture is compressed into a tableted multiple unit effervescent dosage form. With the expression "units" is meant small beads, particles, granules or pellets, in the following referred to as pellets. All of or parts of the effervescent constituents may be granulated before compression or directly compressed together with the enteric coating layered units.

The compaction process (compression) for formulating the tableted multiple unit effervescent dosage form must not significantly affect the acid resistance of the enteric coating layered pellets. In other words the mechanical properties, such as the flexibility and hardness as well as the thickness, of the enteric coating layer(s) must secure that the requirements on enteric coated articles in the United States Pharmacopeia USP are accomplished and the acid resistance does not decrease more than 10% during the compression of pellets into tablets.

The acid resistance is defined as the amount of active substance in tablets or pellets after being exposed to simulated gastric fluid, USP, or to 0.1 M HCl(aq) relative to that of unexposed tablets or pellets, respectively. The test is accomplished in the following way. Tablets or pellets are exposed to simulated gastric fluid at a temperature of 37°C. The tablets disintegrate and release the enteric coated pellets to the medium. After two hours the enteric coated pellets are removed and analyzed for active substance content using High Performance Liquid Chromatography (HPLC).

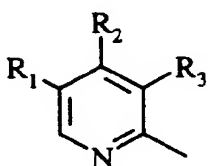
Active substances

The proton pump inhibitors are for example compounds of the general formula I

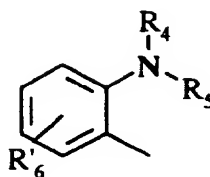


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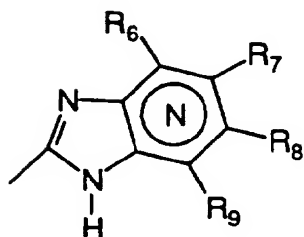
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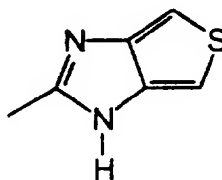
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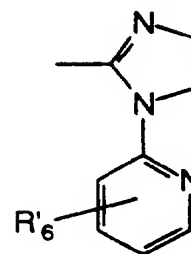
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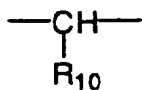
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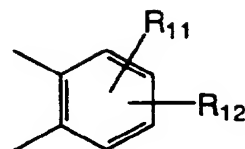
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X =



or



wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R₆-R₉ optionally may be exchanged for a nitrogen atom without any substituents;

R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

5

R₄ and R₅ are the same or different and selected from hydrogen, alkyl and aralkyl;

R'₆ is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

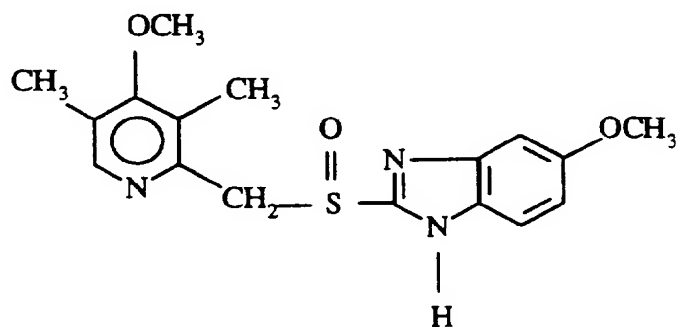
R₆-R₉ are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-
10 alkoxy, alkylcarbonyl, alkoxy carbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R₆-R₉ form ring structures which may be further substituted;

R₁₀ is hydrogen or forms an alkylene chain together with R₃ and

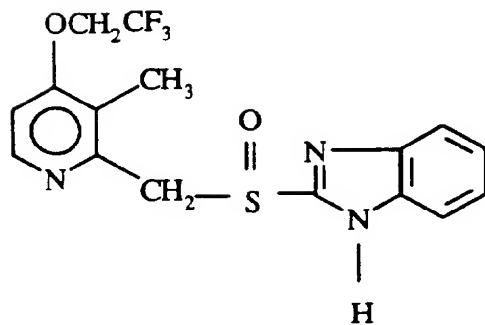
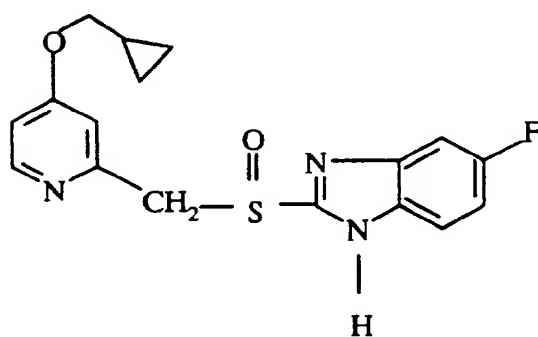
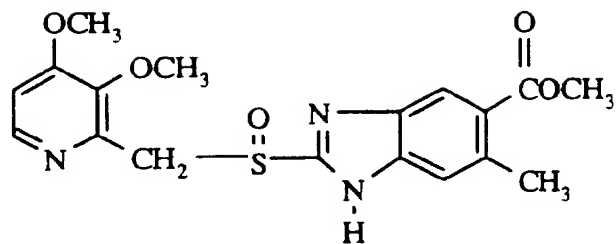
15 R₁₁ and R₁₂ are the same or different and selected from hydrogen, halogen or alkyl and alkyl groups, alkoxy groups and moieties thereof may be branched and straight C₁-C₉-chains or comprise cyclic alkyl groups, for example cycloalkylalkyl.

Examples of proton pump inhibitors according to formula I are

20

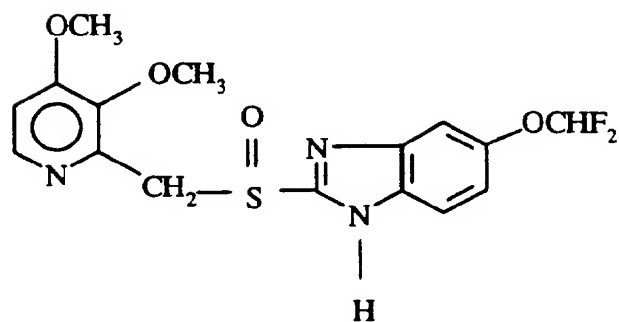


Omeprazole

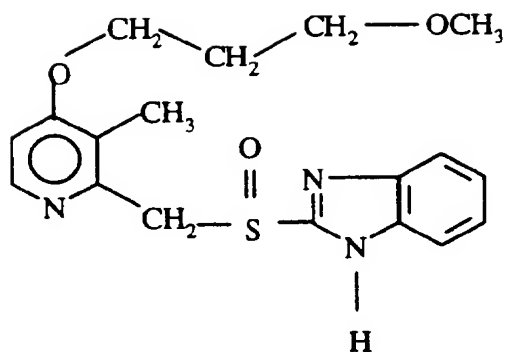


Lansoprazole

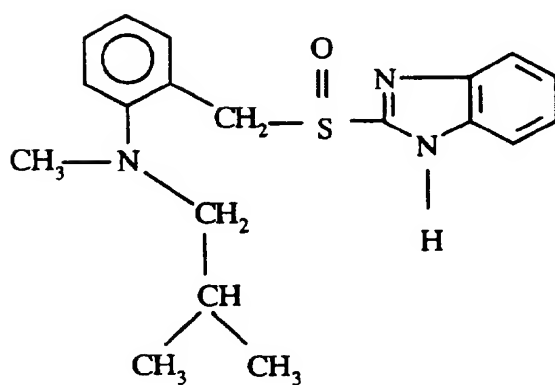
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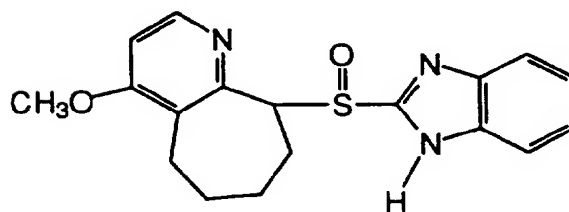
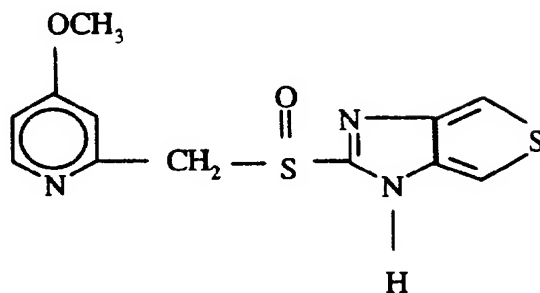
Pantoprazole

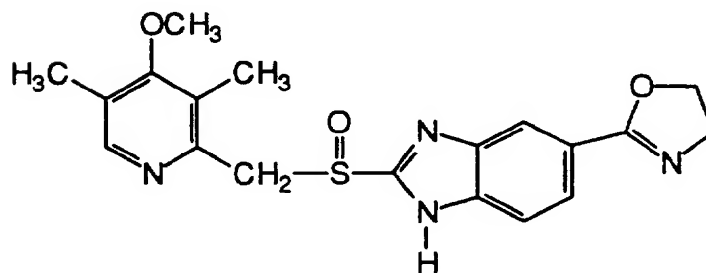
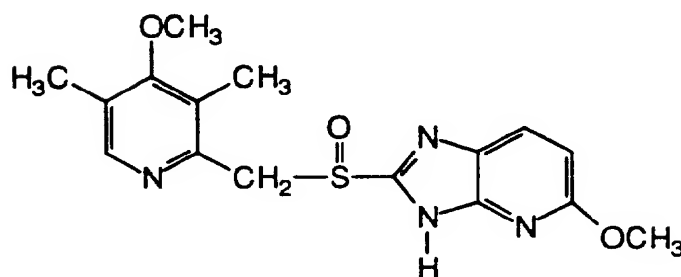
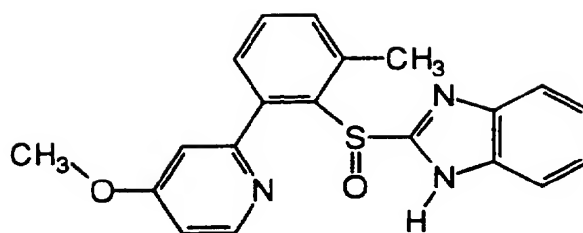


Pariprazole



Leminoprazole





5

The proton pump inhibitors used in the dosage forms of the invention may be used in neutral form or in the form of an alkaline salt, such as for instance the Mg^{2+} , Ca^{2+} , Na^+ , K^+ or Li^+ salts, preferably the Mg^{2+} salts. Further where applicable, the compounds listed
10 above may be used in racemic form or in the form of a substantially pure enantiomer thereof, or alkaline salts of the single enantiomers.

Suitable proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO90/06925, WO91/19711,
15 WO91/19712, and further especially suitable compounds are described in WO95/01977 and WO94/27988.

The effervescent tablet constituents used in the tableted dosage form according to the present invention must not interfere in a disadvantageous manner with the active substance in the prepared tablet. Thus, the buffering components in the effervescent system should, dissolved in water, result in a solution with a pH value that is below the pKa of the enteric coating polymer used on the individually enteric coating layered units comprising the acid susceptible proton pump inhibitor. In most cases the pH value of the obtained solution/dispersion formed upon effervescence should be below 5.5, but depends on the specific enteric coating polymer used. The pH is important to ensure that the enteric coating layer of the units remain intact during the administration to protect the acid susceptible proton pump inhibitor during passage of the stomach, and later disintegrate/dissolve in the small intestine where dissolution of the active substance is desired.

The buffering components of the effervescent constituents can generally be divided in two categories; a carbon dioxide source and an acidic component. The latter reacts with the carbon dioxide source resulting in the development of carbon dioxide gas. The effervescent constituents may also include other tableting excipients such as for instance binding agents, diluents, lubricants, disintegrating agents, surfactants, taste improving agents, colorants or the like.

As carbon dioxide source can be used for instance alkali metal carbonates or bicarbonates, alkaline earth metal carbonates or bicarbonates, or other inorganic salts containing carbonate or bicarbonate ions.

Acidic components suitable to incorporate in an effervescent tablet are preferably solid acidic compounds and include for instance monosodium dihydrogen phosphate, or tartaric acid, citric acid and other weak organic acids.

Further components used in the preparation according to the present invention are described more in detail below.

Core material - containing an acid susceptible proton pump inhibitor.

The core material for the individually enteric coated pellets can be constituted according to different principles. Inert seeds layered with active substance, optionally mixed with alkaline
5 reacting compounds, can be used as the core material for the further processing.

The seeds which are to be layered with the acid susceptible proton pump inhibitor can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or in mixtures or water-soluble seeds comprising different inorganic salts,
10 sugars, non-pareils and other materials, alone or in mixtures. Further, the seeds may comprise the proton pump inhibitor in the form of crystals, agglomerates, compacts etc. The size of the seeds is not essential for the present invention but may vary between approximately 0.1 and 2 mm. The seeds layered with the proton pump inhibitor are produced either by powder or solution/suspension layering using for instance granulation or
15 spray coating layering equipment.

Before the seeds are layered the active substance may be mixed with further components. Such components can be binders, surfactants, fillers, disintegrating agents, alkaline reacting additives or other pharmaceutically acceptable ingredients, alone or in mixtures. The binders
20 are for example polymers such as hydroxypropyl methylcellulose, hydroxypropyl cellulose and carboxymethylcellulose sodium, polyvinyl pyrrolidone, sugars, starches or other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic or ionic surfactants such as for instance sodium lauryl sulfate.

25 Alternatively, the core material can be prepared as substantially homogeneous cores containing omeprazole or one of its single enantiomers or an alkaline salt of omeprazole or one of its single enantiomers mixed with suitable constituents, optionally mixed with alkaline reacting compounds. Said core materials may be produced by
30 extrusion/spheronization, balling or compression utilizing different process equipments.

The size of the formulated homogeneous core material is approximately between 0.1 and 4 mm and preferably between 0.1 and 2 mm. The manufactured homogeneous core materials can be further layered with additional ingredients comprising active substance and/or used for further processing.

5

The active substance is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and a suitable concentration of active substance in the final mixture. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives, can be used.

10

The active substance may also be mixed with an alkaline reacting pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not restricted to, substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

15
20

Alternatively, the aforementioned core material can be prepared by using spray drying or spray congealing technique.

25 The active substance is in the form of an acid labile H^+K^+ ATPase inhibitor according to formula I or an alkaline salt thereof or one of its single enantiomers. These compounds have an asymmetric centre in the sulfur atom, i.e. exists as two optical isomers (enantiomers). Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixtures of the two enantiomers are suitable for the pharmaceutical formulation according to the present invention.

30

Enteric coating layer(s) - for enteric coating layering of the core material of a proton pump inhibitor.

- 5 Before applying enteric coating layer(s) onto the core material in the form of individual pellets, said pellets may optionally be covered with one or more separating layers comprising pharmaceutical excipients optionally including pH-buffering, alkaline compounds. This/these separating layer(s) separate(s) the core material from the outer layer(s) being enteric coating layer(s). The separating layer(s) protecting the core material
10 of a proton pump inhibitor should be water soluble or rapidly disintegrating in water.

The separating layer(s) can be applied on to the core material by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating process. As an alternative
15 the separating layer(s) can be applied to the core material by using coating technique. The materials for separating layers are chosen among the pharmaceutically acceptable compounds such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose sodium and others, used alone or in
20 mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be included into the separating layer(s).

When the optional separating layer(s) is applied to the core material it may constitute a
25 variable thickness. The maximum thickness of the optional separating layer(s) is normally only limited by processing conditions. The separating layer(s) may serve as a diffusion barrier and may act as a pH-buffering zone. The pH-buffering properties of the separating layer(s) can be further strengthened by introducing into the layer(s) substances chosen from a group of compounds usually used in antacid formulations such as, for instance,
30 magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance

$\text{Al}_2\text{O}_3.6\text{MgO.CO}_2.12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3.4\text{H}_2\text{O})$, $\text{MgO.Al}_2\text{O}_3.2\text{SiO}_2.n\text{H}_2\text{O}$, aluminium hydroxide/sodium bicarbonate coprecipitate or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, carbonic, citric or other suitable, weak, inorganic or organic acids; or suitable organic bases, including basic amino acids and salts thereof. Talc or other compounds may be added to increase the thickness of the layer(s) and thereby strengthen the diffusion barrier. The optionally applied separating layer(s) is not essential for the invention. However the separating layer(s) may improve physical and chemical properties of the novel multiple unit tableted dosage form.

Alternatively, the separating layer may be formed *in situ* by a reaction between an enteric coating polymer layer applied on the core material and an alkaline reacting compound in the core material. Thus, the separating layer formed comprises a water soluble salt formed between the enteric coating layer polymer(s) and an alkaline reacting compound which is in the position to form a salt.

One or more enteric coating layers are applied onto the core material or onto the core material covered with separating layer(s) by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in suitable organic solvents. As enteric coating layer polymers one or more, separately or in combination, of the following can be used; e.g. solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating layer polymer(s).

The enteric coating layers contain pharmaceutically acceptable plasticizers to obtain the desired mechanical properties, such as flexibility and hardness of the enteric coating layers. Such plasticizers are for instance, but not restricted to, cetanol, triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, polyethylene glycol, polysorbates or other plasticizers.

The amount of plasticizer is optimized for each enteric coating layer formula, in relation to selected enteric coating layer polymer(s), selected plasticizer(s) and the applied amount of said polymer(s), in such a way that the mechanical properties, i.e. flexibility and hardness of the enteric coating layer(s), for instance exemplified as Vickers hardness are adjusted so that the acid resistance of the pellets covered with enteric coating layer(s) does not decrease significantly during the compression of pellets into tablets. The amount of plasticizer is usually in the range of 1-50 % by weight of the enteric coating layer polymer(s), preferably 10 - 50 % and more preferably 15 - 50 %. Additives such as dispersants, colorants, pigments, polymers e.g. poly(ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be included into the enteric coating layer(s). Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acid susceptible material.

To protect an acid susceptible proton pump inhibitor and to obtain an acceptable acid resistance of the multiple unit tableted dosage form, according to the invention the enteric coating layer(s) constitutes a thickness of approximately at least 10 μm , preferably more than 20 μm . The maximum thickness of the applied enteric coating layer(s) is normally limited by processing conditions, and the desired dissolution profile.

Over-coating layer

Pellets covered with enteric coating layer(s) may further be covered with one or more over-coating layer(s). This over-coating layer(s) should be water soluble or rapidly disintegrating in water. The over-coating layer(s) can be applied to the core material by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating process. The materials for over-coating layers are chosen among the pharmaceutically acceptable compounds such as, for instance sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose sodium and others, used alone or in

mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be included into the over-coating layer(s). Said over-coat may further prevent potential agglomeration of coated pellets, protect the enteric coating towards cracking during the compaction process and enhance compressability during tableting. The maximum thickness of the applied over-coating layer(s) is normally limited by processing conditions, and the desired dissolution profile. The above described over-coating layer may also be used as a tablet coating layer to obtain tablets of good appearance.

10 Effervescent preparation

The effervescent constituents can be dry mixed, wet granulated, compacted, melt granulated or prepared according to any known granulation technique. When wet granulated the acidic component may be granulated separately or in combination with the carbon dioxide source. If granulated in combination, it is advantageous to use a granulation liquid that contains as little water as possible, e.g. ethanol 99 %.

Effervescent tablets

20 The enteric coating layered pellets comprising an acid susceptible proton pump inhibitor are mixed with effervescent constituents and optionally with tablet excipients such as fillers, binders, disintegrants, lubricants and other pharmaceutical acceptable additives and compressed into a multiple unit tableted dosage form according to the present invention. The proton pump inhibitor as well as the effervescent constituents are defined above.

25

By choosing small enteric coated pellets in the formulation according to the present invention, the fraction of pellets in each tablet can be held high and the pellets evenly distributed within the tablet and easily dispersible upon effervescence.

30 Thus, the formulation according to the invention consists of core material containing an active substance, optionally mixed with alkaline reacting compound(s), and tablet

excipients. The addition of an alkaline reacting material may not be necessary, but such a substance may further enhance the stability of the active substance. The core material is optionally coated with one or more separating layer(s) optionally containing pH-buffering substance(s). The pellets, optionally covered with a separating layer(s), are then covered with one or more enteric coating(s) rendering the pellets being insoluble in acidic media, but disintegrating/ dissolving in near neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine where dissolution is desired. The enteric coating layered pellets may further be covered with an over-coat before formulated together with the effervescent constituents into the tableted multiple unit effervescent dosage form as mentioned above.

Process

The process for the manufacture of the dosage form represents a further aspect of the invention. The pharmaceutical processes can preferably be completely water-based and different ways to practice the invention are described in the accompanying examples below.

Use of preparation

The preparation according to the invention is especially advantageous in reducing gastric acid secretion. It is administered one to several times a day, preferable once or twice daily. The typical daily dose of the active substance varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general the daily dose will be in the range of 1-1000 mg of active substance. Preferred dosages are 10-100 mg of the proton pump inhibitor.

The present invention is described in more detail by the following non-limiting example.

Example 1.

Effervescent tablets containing 20 mg omeprazole.

Manufacturing of pellets containing magnesium omeprazole.

Core material

5	Magnesium omeprazole	12.00 kg
	Non-pareil cores	12.00 kg
	Hydroxypropyl methylcellulose	1.8 kg
	Water purified	35.4 kg

10 Separating layer

	Core material (acc. to above)	23.50 kg
	Hydroxypropyl cellulose	2.35 kg
	Talc	4.03 kg
	Magnesium Stearate	0.34 kg
15	Water purified	48.00 kg

Enteric coating layer

	Pellets with a sep layer (acc. to above)	29.00 kg
	Methacrylic acid copolymer (30% suspension)	38.70 kg
20	Triethyl citrate	3.48 kg
	Mono- and diglycerides (NF)	0.58 kg
	Polysorbate 80	0.06 kg
	Water purified	22.68 kg

25 Over-coating layer

	Enteric coated pellets (acc. to above)	44.7 kg
	Hydroxypropyl methylcellulose	0.58 kg
	Mg-Stearate	0.02 kg
	Water purified	11.6 kg

Suspension layering was performed in a fluid bed apparatus. Magnesium omeprazole was sprayed onto inert suger seeds (non-parcil cores) from a water suspension containing the dissolved binder.

- 5 The prepared core material was coating layered with a separating layer in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethylcitrate and polysorbate was sprayed onto the pellets (layered with a separating layer) in a fluid bed apparatus. In the same type of apparatus the enteric coating layered pellets
10 were coated with hydroxypropyl methylcellulose/Mg-stearate suspension. The pellets covered by an over-coating layer were classified by sieving.

The obtained enteric coating layered pellets were mixed with prepared granules and other components as described below and thereafter compressed to effevescent tablets.

15

Granulation (1 000 tablets);

	Citric acid anhydrous	605	g
	Mannitol dried	200	g
	Riboflavine	0.1	g
20	Polyvinylpyrrolidone K-25 (PVP K-25)	6.0	g
	EtOH 99%(w/v)	90	g

- The PVP K-25 was dissolved in the ethanol to give the granulating solution. In this solution the riboflavine was dispersed. The citric acid and mannitol were mixed and the liquid was
25 added and the mass further mixed. Then the mass was put on a tray and dried in a drying oven for approx. 2 hrs at 55 degrees Celsius. The granulate was milled to pass sieve 1.0 mm.

A pre-mix consisting of the following was prepared by dry mixing in a turbula mixer;

30

	Sodium carbonate anhydrous	36 g
	Sodium dodecyl sulphate	1 g
	Sodium stearyl fumarate	14 g
	Essence orange	2.0 g
5	Saccharine Sodium	2.0 g
	Polyvinyl pyrrolidone cross-linked	70 g
	Enteric coated pellets from above	95.7 g

Final mixing was performed in a Kenwood mixer where the following ingredients were dry
10 mixed:

	Granulate from above	811.1 g
	Premix from above	220.7 g
	Sodium bicarbonate	453 g

15

The final mixing time was 4 minutes.

20

Compression to tablets was done on a tableting machine equipped with punches giving 20 mm diameter flat tablets with bevelled edges.

Tablet weight was 1485 mg. The compressed tablets had an average height of 3.6 mm (n=10). The effervescence time of the tablets was measured by placing the tablet in a basket of metal wiring and then immersing the basket in 300 ml of water at 20 degrees Celsius. The effervescence time was considered finished when there was no material left in
25 the immersed basket. For this tablet composition the time was 30 seconds.

One tablet was placed in 100 ml purified water. The pH of the obtained dispersion was 4.8. Another tablet was exposed for 0.1 M HCl during 2 hours. The liberated enteric coated units were transferred to phosphate buffer solution of pH 6.8. After 30 min 91 % of the
30 omeprazole dose was found in the solution.

Example 2

Preparation of enteric coating layered pellets containing lansoprazole.

5 Core material

Non-pareil cores	400	g
Lansoprazole	400	g
Hydroxypropyl methylcellulose	80	g
Sodium laurylsulphate	3	g
10 Water purified	1360	g

Separating layer

Core material (acc. to above)	100	g
Hydroxypropyl methylcellulose	9	g
15 Polyethyleneglycol 6000	1	g
Talc	18	g
Ethanol 95%	250	g
Water purified	250	g

20 Enteric coating layer

Sub-coated pellets (acc. to above)	100	g
Hydroxypropyl methylcellulose phtalate	40	g
Acetyltributyl citrate	8	g
Cetanol	2	g
25 Ethanol 95%	162	g
Acetone	378	g

Suspension layering was performed in a Wurster equipped fluid bed apparatus.

Lansoprazole was sprayed onto inert non-pareil cores from a water suspension containing lansoprazole, the dissolved binder and the wetting agent.

- 5 The prepared core material was coating layered with a separating layer in the same equipment by spraying a suspension of talc in a HPMC/PEG- solution. PEG was added to act as a plasticizer for the HPMC.

- 10 Enteric coating layer was applied in the same equipment by spraying the enteric coating polymer solution (including additives according to above) onto the pellets (layered with a separating layer). The obtained enteric coating layered pellets were mixed with prepared granules and other component as described in example 1, and compressed into effervescent tablets.

15 Example 3

Effervescent tablets 20 mg containing 20 mg omeprazole

Manufacturing of pellets.

20 Core material

Suspension for layering

Magnesium omeprazole	5.0 kg
Hydroxypropyl methylcellulose	0.8 kg
Water purified	14.3 kg

25

Seeds for layering

Non-pareil cores	10.0 kg
------------------	---------

- 30 The active substance was suspended in a solution prepared of the hydroxypropyl methylcellulose in the water, and thereafter homogenized in a ball mill.

The suspension was sprayed onto the seeds in a Wurster equipped fluidized bed apparatus.

Separating layer

	Core material (acc. to above)	14.6 kg
5	Hydroxypropyl cellulose	1.5 kg
	Talc	2.5 kg
	Magnesium Stearate	0.2 kg
	Water purified	29.2 kg

- 10 The talc and magnesium stearate were suspended in a solution prepared by dissolving the hydroxypropyl cellulose in the water. The suspension was sprayed onto the core material in the same equipment as above.

Enteric coating layer

15	Prepared pellets (acc. to above)	250 g
	Methacrylic acid copolymer (30% suspension)	458 g
	Triethyl citrate	41 g
	Titanium dioxide	19 g
20	Mono- and diglycerides (NF)	7 g
	Polysorbate 80	0.7 g
	Water purified	329 g

- 25 The pH of the methacrylic acid copolymer coating suspension was first adjusted to 4.0 by adding 14 ml of 0.5 M sodium hydroxide solution. Thereafter all of the triethylcitrate was added. (= Suspension A.)

- 30 The polysorbate 80 was mixed with 120 g of water, whereafter the mono- and diglycerides was added and this mixture was heated to above 70°C for 10 minutes and the cooled during agitation to room temperature. (= Emulsion B.)

The titanium dioxide was suspended in 120 g of water. The pH of the suspension was 4.4.
(= Suspension C.)

- 5 The emulsion B, the suspension C and 89 g of water were added to suspension A. The pH of the mixture was checked and found to be 4.2.

(At pH below 4.5 this enteric coating suspension showed no signs of precipitation.)

- 10 The suspension (during agitation with a magnetic stirrer) was sprayed onto the core material in a Wurster equipped fluidized bed apparatus.

The obtained enteric coated pellets were mixed with powders and effervescent granules and thereafter compressed to effervescent tablets.

15

Effervescent granules;

	Citric acid anhydrous	11.4 kg
	Sodium bicarbonate	8.4 kg
20	Polyvinylpyrrolidone K-25 (PVP K-25)	0.3 kg
	EtOH 99%(w/v)	0.8 kg
	water purified	0.3 kg

- 25 The PVP K-25 was dissolved in the ethanol + water to give the granulating solution. This solution was used to granulate the citric acid sodium bicarbonate mixture. The wet mass was dried at 55°C, and after cooling to room temperature the granulate was milled to pass sieve 1.1 mm.

A pre-mix (for 400 tablets) was prepared by dry mixing in a Kenwood mixer the following;

27

Sodium carbonate anhydrous	38	g
Sorbitol	160	g
Antifoam M	5.8	g

- 5 The premix was passed through a 0.5 mm sieve.

Final mixing (for 400 tablets) was performed in the same Kenwood mixer where the following ingredients were dry mixed:

10 Effervescent granules from above	909	g
Premix from above	204	g
Sodium steryl fumarate (passing sieve 0.5 mm)	7	g
Enteric coated pellets from above	70	g

- 15 Compression to tablets was done on a tableting machine equipped with punches giving 25 mm diameter flat tablets.

Tablet weight was 2970 mg. The compressed tablets had an average height of 4.3 mm (n=4) and an average hardness of 77 N (n= 10). The effervescence time of the tablets was
20 measured by putting the tablet in a basket of metal wiring and then immersing the basket in 150 ml of water (20 degrees Celsius). The effervescence time was considered finished when there was no material left in the immersed basket. For this tablet composition the time was 55 seconds.

- 25 The pH of the obtained dispersion testing in the tablet in 150 ml purified water was 5.0.

Gastric juice resistance (determined as % of the dose omeprazole remaining after exposure for 0.1 M HCl during 2 hours) was 91%.

Example 4

Effervescent tablets containing 40 mg omeprazole.

Manufacturing of pellets.

5

Core materialSuspension for layering

	Magnesium omeprazole	5.5 kg
	Hydroxypropyl methylcellulose	0.8 kg
10	Water purified	15.7 kg

Seeds for layering

	Non-pareil cores	11.0 kg
--	------------------	---------

- 15 The active substance was suspended in a solution prepared of the hydroxypropyl methylcellulose in the water, and thereafter homogenized in a ball mill.
The suspension was sprayed onto the seeds in a Wurster equipped fluidized bed apparatus.

Separating layer

20	Core material (acc. to above)	16.0 kg
	Hydroxypropyl cellulose	1.6 kg
	Talc	2.7 kg
	Magnesium Stearate	0.2 kg
	Water purified	32 kg

25

The talc and magnesium stearate were suspended in a solution prepared by dissolving the hydroxypropyl cellulose in the water. The suspension was sprayed onto the core material in the same equipment as above.

Enteric coating layer

	Prepared Pellets (acc. to above)	20 kg
	Methacrylic acid copolymer (30% dispersion)	33 kg
	Triethyl citrate	3 kg
5	Mono- and diglycerides (NF)	0.5 kg
	Polysorbate 80	0.05kg
	Water purified	20.5 kg

10 The methacrylic acid copolymer dispersion was mixed with 1.0 kg of water and the triethylcitrate during agitation. (= Dispersion A.)

The polysorbate 80 was mixed with 19.5 kg of water, whereafter the mono- and diglycerides was added and this mixture was heated to above 70°C for 10 minutes and the cooled during agitation to room temperature. (= Emulsion B.)

15

The emulsion B was added to suspension A and mixed to homogeneity.

The suspension (during agitation with a magnetic stirrer) was sprayed onto the core material in a Wurster equipped fluidized bed apparatus.

20

Directly after the enteric coating dispersion was applied, the pellets in the fluidized bed were sprayed with a hydroxypropyl methylcellulose solution containing magnesium stearate dispersed therein to accomplish an overcoating layer.

The composition of the dispersion was;

25

Water purified	8.0 kg
Hydroxypropyl methylcellulose	0.4 kg
Magnesium stearate	0.01 kg

The obtained (overcoated) enteric coated pellets were mixed with powders and effervescent granules and thereafter compressed to effervescent tablets.

5 Effervescent granules;

	Citric acid anhydrous	11.4	kg
	Sodium bicarbonate	8.4	kg
	Polyvinylpyrrolidone K-25 (PVP K-25)	0.3	kg
	EtOH 99%(w/v)	0.8	kg
10	water purified	0.3	kg

The PVP K-25 was dissolved in the ethanol + water to give the granulating solution. This solution was used to granulate the citric acid sodium bicarbonate mixture. The wet mass was dried at 55°C and after cooling to room temperature the granulate was milled to pass
15 sieve 1.1 mm.

A pre-mix (for 400 tablets) was prepared by dry mixing in a Kenwood mixer the following;

	Sodium carbonate anhydrous	38	g
20	Sorbitol	160	g
	Antifoam M	5.8	g

The premix was passed through a 0.5 mm sieve.

25 Final mixing (for 400 tablets) was performed in the same Kenwood mixer where the following ingredients were dry mixed:

	Effervescent granules from above	910	g
	Premix from above	204	g
30	Sodium steryl fumarate (passing sieve 0.5 mm)	7	g

Enteric coated pellets from above 128 g

Compression to tablets was done on a tableting machine equipped with punches giving 25 mm diameter flat tablets.

5

Tablet weight was 3120 mg. The compressed tablets had an average height of 4.6 mm (n=4) and an average hardness of 67 N (n= 10). The effervescence time of the tablets was measured by putting the tablet in a basket of metal wiring and then immersing the basket in 150 ml of water (20 degrees Celsius). The effervescence time was considered finished when there was no material left in the immersed basket. For this tablet composition the time was 55 seconds.

10

The pH of the obtained dispersion when testing the tablet in 150 ml purified water was 5.0. Gastric juice resistance (determined as % of the dose omeprazole remaining after exposure for 0.1 M HCL during 2 hours) was 94%.

15

Example 5

Effervescent tablets containing 60 mg omeprazole.

20 Manufacturing of pellets.

Core material

Suspension for layering

Magnesium omeprazole	5.5 kg
25 Hydroxypropyl methylcellulose	0.8 kg
Water purified	15.7 kg

Seeds for layering

Non-pareil cores	11.0 kg
------------------	---------

30

The active substance was suspended in a solution prepared of the hydroxypropyl methylcellulose in the water, and thereafter homogenized in a ball mill.

The suspension was sprayed onto the seeds in a Wurster equipped fluidized bed apparatus.

5 Separating layer

	Core material (acc. to above)	16 kg
	Hydroxypropyl cellulose	1.6 kg
	Talc	2.7 kg
	Magnesium Stearate	0.2 kg
10	Water purified	32 kg

The talc and magnesium stearate were suspended in a solution prepared by dissolving the hydroxypropyl cellulose in the water. The suspension was sprayed onto the core material in the same equipment as above.

15

Enteric coating layer

	Prepared pellets (acc. to above)	20 kg
	Methacrylic acid copolymer (30% dispersion)	33 kg
20	Triethyl citrate	3 kg
	Mono- and diglycerides (NF)	0.5 kg
	Polysorbate 80	0.05kg
	Water purified	20.5 kg

25 The methacrylic acid copolymer dispersion was mixed with 1.0 kg of water and the triethylcitrate during agitation. (= Dispersion A.)

The polysorbate 80 was mixed with 19.5 kg of water, whereafter the mono- and diglycerides was added and this mixture was heated to above 70°C for 10 minutes and the
30 cooled during agitation to room temperature. (= Emulsion B.)

The emulsion B was added to suspension A and mixed to homogeneity.

The suspension (during agitation with a magnetic stirrer) was sprayed onto the core material
5 in a Wurster equipped fluidized bed apparatus.

Directly after the enteric coating dispersion was applied, the pellets in the fluidized bed were
sprayed with a hydroxypropyl methylcellulose solution containing magnesium stearate
dispersed therein to accomplish an overcoating layer.

10 The composition of the dispersion was;

Water purified	8 kg
Hydroxypropyl methylcellulose	0.4 kg
Magnesium stearate	0.01kg

15

The obtained (overcoated) enteric coated pellets were mixed with powders and effervescent
granules and thereafter compressed to effervescent tablets.

20 Effervescent granules;

Citric acid anhydrous	11.4 kg
Sodium bicarbonate	8.4 kg
Polyvinylpyrrolidone K-25 (PVP K-25)	0.3 kg
EtOH 99%(w/v)	0.8 kg
25 water purified	0.3 kg

The PVP K-25 was dissolved in the ethanol + water to give the granulating solution. This
solution was used to granulate the citric acid sodium bicarbonate mixture. The wet mass
was dried at 55°C and after cooling to room temperature the granulate was milled to pass
30 sieve 1.1 mm.

A pre-mix (for 400 tablets) was prepared by dry mixing in a Kenwood mixer the following:

	Sodium carbonate anhydrous	38 g
5	Sorbitol	160 g
	Antifoam M	5.8 g

The premix was passed through a 0.5 mm sieve.

- 10 Final mixing (for 400 tablets) was performed in the same Kenwood mixer where the following ingredients were dry mixed:

	Effervescent granules from above	910 g
	Premix from above	204 g
15	Sodium steryl fumarate (passing sieve 0.5 mm)	7 g
	Enteric coated pellets from above	191 g

Compression to tablets was done on a tableting machine equipped with punches giving 25 mm diameter flat tablets.

20

Tablet weight was 3230 mg. The compressed tablets had an average height of 4.9 mm (n=4) and an average hardness of 51 N (n= 10). The effervescence time of the tablets was measured by putting the tablet in a basket of metal wiring and then immersing the basket in 150 ml of water (20 degrees Celsius). The effervescence time was considered finished when
25 there was no material left in the immersed basket. For this tablet composition the time was 58 seconds.

The pH of the obtained dispersion when testing a tablet in 150 ml purified water was 5.0. Gastric juice resistance (determined as % of the dose omeprazole remaining after exposure
30 for 0.1 M HCl during 2 hours) was 94%....

Example 6

Effervescent tablets containing 20 mg S-omeprazole magnesium salt.

5 **Manufacturing of pellets.**Core materialSuspension for layering

	S-omeprazole magnesium	300	g
10	micronized.		
	Hydroxypropyl methylcellulose	75	g
	Water purified	1425	g

Seeds for layering

15	Non-pareil cores	300	g
----	------------------	-----	---

The active substance was suspended in a solution prepared of the hydroxypropyl methylcellulose in the water. The suspension was sprayed onto the seeds in a Wurster equipped fluidized bed apparatus.

20

Separating layer

	Core material (acc. to above)	294	g
	Hydroxypropyl cellulose	29	g
	Talc	50	g
25	Magnesium Stearate	4	g
	Water purified	588	g

The talc and magnesium stearate were suspended in a solution prepared by dissolving the hydroxypropyl cellulose in the water. The suspension was sprayed onto the core material in
30 the same equipment as above.

Enteric coating layer

	Prepared pellets (acc. to above)	300	g
5	Methacrylic acid copolymer (30% dispersion)	400	g
	Triethyl citrate	36	g
	Mono- and diglycerides (NF)	6	g
	Polysorbate 80	0.6	g
	Water purified	235	g

10

The methacrylic acid copolymer dispersion was mixed with the triethylcitrate during agitation. (= Dispersion A.)

15

The polysorbate 80 and the mono-and diglycerides were mixed with the water, whereafter this mixture was heated to above 70°C for 10 minutes and emulsified in a mixer. Then it was cooled during agitation to room temperature. (= Emulsion B.)

The emulsion B was added to Dispersion A and mixed to homogeneity.

20

The obtained dispersion was sprayed onto the core material in a Wurster equipped fluidized bed apparatus.

25

Directly after the enteric coating dispersion was applied, the pellets in the fluidized bed were sprayed with a hydroxypropyl methylcellulose solution containing magnesium stearate dispersed therein to accomplish an overcoating layer.

The composition of this dispersion was;

30

	Water purified	120	g
	Hydroxypropyl methylcellulose	6	g
	Magnesium stearate	0.3	g

Preparation of effervescent tablets.

The obtained (overcoated) enteric coated pellets were mixed with powders and effervescent granules and thereafter compressed to effervescent tablets.

5

Effervescent granules;

	Citric acid anhydrous	11.4 kg
	Sodium bicarbonate	8.4 kg
	Polyvinylpyrrolidone K-25 (PVP K-25)	0.3 kg
10	EtOH 99%(w/v)	0.8 kg
	water purified	0.3 kg

The PVP K-25 was dissolved in the ethanol + water to give the granulating solution. This solution was used to granulate the citric acid sodium bicarbonate mixture. The wet mass was dried at 55°C and after cooling to room temperature the granulate was milled to pass sieve 1.1 mm.

15

A pre-mix (for 50 tablets) was prepared by dry mixing in a mixer the following;

20	Sodium carbonate anhydrous	4.8 g
	Sorbitol	20 g
	Antifoam M	0.7 g

The premix was passed through a 0.5 mm sieve.

25

Final mixing (for 50 tablets) was performed in the same mixer where the following ingredients were dry mixed:

	Effervescent granules from above	114 g
30	Premix from above	25.5 g

Sodium steryl fumarate (passing sieve 0.5 mm)	0.9 g
Enteric coated pellets from above	4.7 g

Compression to tablets was done on a tableting machine equipped with punches giving 25
5 mm diameter flat tablets.

Tablet weight was 2890 mg. The compressed tablets had an average height of 4.2 mm
(n=4) and an average hardness of 100 N (n= 5). The effervescence time of the tablets were
measured by putting the tablet in a basket of metal wiring and then immersing the basket in
10 150 ml of water (20 degrees Celsius). The effervescence time was considered finished when
there was no material left in the immersed basket. For this tablet composition the time was
55 seconds.

The pH of the obtained dispersion when testing in a tablet in 150 ml purified water was 5.0.
15

Gastric juice resistance (determined as % of the dose S-omeprazole remaining after
exposure for 0.1 M HCl during 2 hours) was 94%.

The enteric coating layered pellets comprising a proton pump inhibitor may also be prepared
20 as described in the following examples.

Example 7

Preparation of enteric coating layered pellets by extrusion/spheronization.

25

Core material

Magnesium omeprazole	600 g
Mannitol	1000 g
Microcrystalline cellulose	300 g
30 Hydroxypropyl cellulose	100 g

Sodium lauryl sulphate	6 g
Water purified	802 g

Separating layer

5	Core material (acc. to above)	400 g
	Hydroxypropyl methylcellulose	48 g
	Water purified	960 g

Enteric coating layer

10	Pellets covered with separating layer (acc. to above)	200 g
	Methacrylic acid copolymer	100 g
	Triethyl citrate	30 g
	Mono- and diglycerides (NF)	5 g
	Polysorbate 80	0.5 g
15	Water purified	309 g

Sodium lauryl sulphate is dissolved in purified water to form the granulation liquid.

Magnesium omeprazole, mannitol, microcrystalline cellulose and hydroxypropyl cellulose are dry-mixed. The granulation liquid is added to the powder mixture and the mass is wet-
20 mixed.

The wet mass is forced through an extruder equipped with screens of size 0.5 mm. The extrudate is spheronized on a friction plate in a spheronizing apparatus. The core material is dried in a fluid bed dryer and classified. The prepared core material is covered by a
25 separating layer in a fluid bed apparatus with a hydroxypropyl methylcellulose/water solution.

The enteric coating layer is applied to the pellets covered with separating layer from an aqueous dispersion of methacrylic acid copolymer plasticized with triethyl citrate to which a
30 mono- and diglycerides/polysorbate dispersion has been added. The pellets are dried in a fluid bed apparatus.

Example 8

Preparation of enteric coating layered pellets by powder layering of sugar sphere seeds.

5

Core material

	Magnesium omeprazole	1 500 g
	Sugar sphere seeds	1 500 g
	Hydroxypropyl methylcellulose	420 g
10	Aerosil®	8 g
	Water purified	4 230 g

Separating layer

	Core material (acc. to above)	500 g
15	Hydroxypropyl cellulose	40 g
	Talc	67 g
	Magnesium stearate	6 g
	Water purified	800 g

20 Enteric coating layer

	Pellets covered with separating layer (acc. to above)	500 g
	Methacrylic acid copolymer	200 g
	Triethyl citrate	60 g
	Water purified	392 g

25

Magnesium omeprazole, part of the hydroxypropyl methylcellulose and Aerosil® are dry-mixed forming a powder. Sugar sphere seeds (0.25-0.40 mm) are layered with the powder in a centrifugal fluidized coating granulator while spraying a hydroxypropyl methylcellulose solution (6 %, w/w).

30

The prepared core material is dried and covered by a separating layer in a centrifugal fluidized coating-granulator. A fluid bed apparatus is used for enteric coating layering.

Example 9

- 5 Preparation of enteric coating layered pellets with silicon dioxide seeds.

Core material

	Magnesium omeprazole	8.0 kg
10	Silicon dioxide	8.0 kg
	Hydroxypropyl methylcellulose	1.4 kg
	Sodium lauryl sulphate	0.1 kg
	Water purified	28.0 kg

15 Separating layer

	Core material (acc. to above)	10.0 kg
	Hydroxypropyl methylcellulose	0.8 kg
	Water purified	10.0 kg

20 Enteric coating layer

	Pellets covered with separating layer (acc. to above)	300 g
	Methacrylic acid copolymer	124 g
	Polyethylene glycol 400	25 g
	Mono- and diglycerides (NF)	3 g
25	Polysorbate 80	1 g
	Water purified	463 g

- Suspension layering is performed in a fluid bed apparatus. Magnesium omeprazole is sprayed onto the silicon dioxide seeds from a water suspension containing the dissolved binder and a surface active ingredient.
- 30

The prepared core material is covered with a separating layer in a fluid bed apparatus with a hydroxypropyl methylcellulose solution. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, polyethylene glycol 400 and polysorbate is sprayed onto the pellets covered with separating layer in a fluid bed apparatus.

5

Example 10

Preparation of enteric coating layered pellets.

10

Enteric coating layer

Pellets covered with separating layer
(manufacturing and composition
as in example 2)

500 g

Methacrylic acid copolymer

250 g

15

Polyethylene glycol 6000

75 g

Mono- and diglycerides (NF)

12.5 g

Polysorbate 80

1.2 g

Water purified

490 g

20

Example 11

Preparation of enteric coating layered pellets.

Enteric coating

25

Pellets covered with separating layer
(manufacturing and composition as in example 1)

500 g

Hydroxypropyl methylcellulose phthalate

250 g

Cetanol

50 g

Ethanol (95%)

1000 g

30

Acetone

2500 g

Example 12

Preparation of enteric coating layered pellets.

5 Core material

Omeprazole	225 g
Mannitol	1425 g
Hydroxypropyl cellulose	60 g
Microcrystalline cellulose	40 g
10 Lactose anhydrous	80 g
Sodium lauryl sulphate	5 g
Disodium hydrogen phosphate dihydrate	8 g
Water purified	350 g

15 Separating layer

Core material (acc. to above)	300 g
Hydroxypropyl cellulose	30 g
Talc	51 g
Magnesium stearate	4 g

20

Enteric coating layer

Pellets covered with separating layer (acc. to above)	300 g
Methacrylic acid copolymer	140 g
Triethyl citrate	42 g
25 Mono- and diglycerides (NF)	7 g
Polysorbate 80	0.7 g

The dry ingredients for producing the core material are well mixed in a mixer. Addition of granulation liquid is made and the mixture is kneaded and granulated to a proper consistency. The wet mass is pressed through an extruder screen and the granules are converted into a spherical form in a spheronizer. The core material is dried in a fluid bed

apparatus and classified into a suitable particle size range, e.g. 0.5 - 1.0 mm. The prepared core material is covered with a separating layer and is enteric coating layered as described in previous examples.

5 **Preparation of active substance.**

Magnesium omeprazole used in some of the examples is produced according to the process described in WO95/01977, the single enantiomers of omeprazole salts are prepared as described in WO94/27988 and omeprazole is produced according to the process disclosed
10 in EP-A1 0005129. These documents are hereby incorporated in a whole by reference.

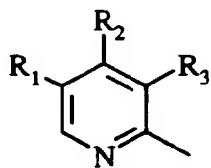
Claims

1. A tableted multiple unit effervescent dosage form comprising effervescent tablet constituents and enteric coating layered units of a core material comprising an acid susceptible proton pump inhibitor in the form of the racemate, an alkaline salt thereof or one of its single enantiomers or an alkaline salt thereof, optionally admixed with alkaline reacting compounds, the core material is coating layered with one or more coating layers, at least one of which is an enteric coating layer, characterized in that the enteric coating layer(s) has mechanical properties such that the compression of the enteric coating layered units with the effervescent tablet constituents into the multiple unit tableted dosage form does not significantly affect the acid resistance of the enteric coating layered units.
2. A tableted effervescent dosage form according to claim 1, wherein the proton pump inhibitor is a compound of the general formula I in the form of the racemate, an alkaline salt or one of its single enantiomers or an alkaline salt thereof

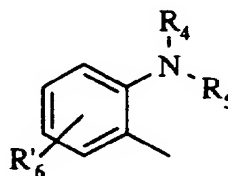


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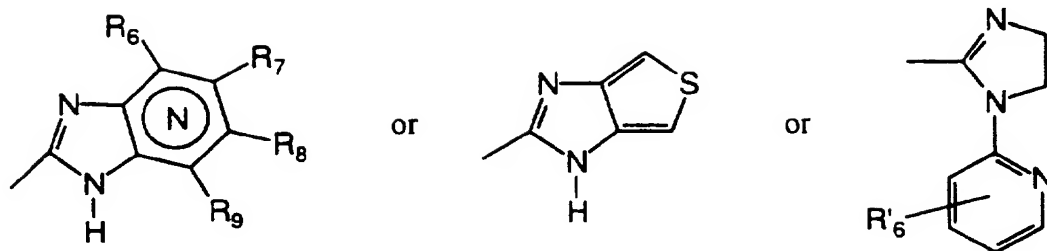
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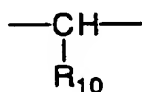
or



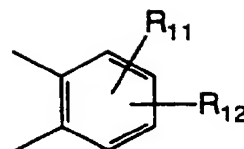
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or



wherein

5

N in the benzimidazole moiety means that one of the carbon atoms substituted by R₆-R₉ optionally may be exchanged for a nitrogen atom without any substituents;

R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

10

R₄ and R₅ are the same or different and selected from hydrogen, alkyl and aralkyl;

R'₆ is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

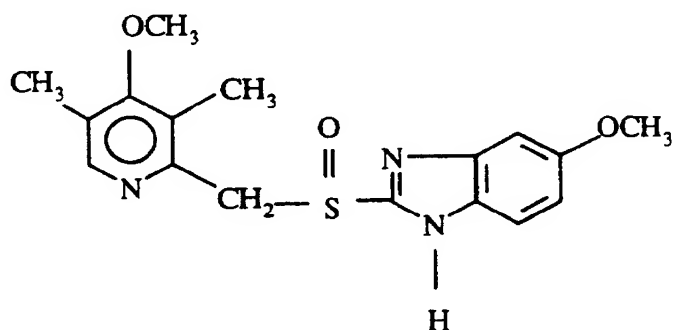
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R₆-R₉ are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R₆-R₉ form ring structures which may be further substituted;

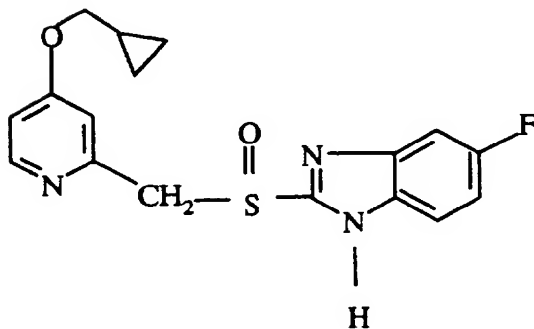
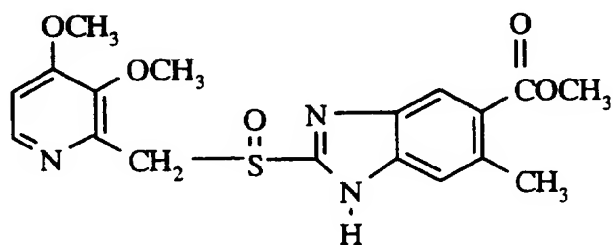
20 R₁₀ is hydrogen or forms an alkylene chain together with R₃ and

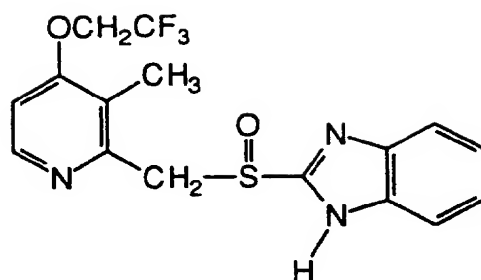
R₁₁ and R₁₂ are the same or different and selected from hydrogen, halogen or alkyl and alkyl groups, alkoxy groups and moities thereof may be branched and straight C₁-C₉-chains or comprise cyclic alkyl groups, for example cycloalkylalkyl.

- 5 3. A tableted effervescent dosage form according to claim 1, wherein the proton pump inhibitor is one of the following compounds

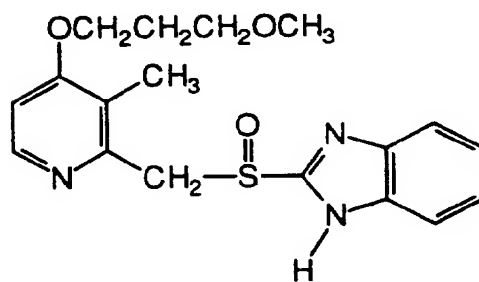
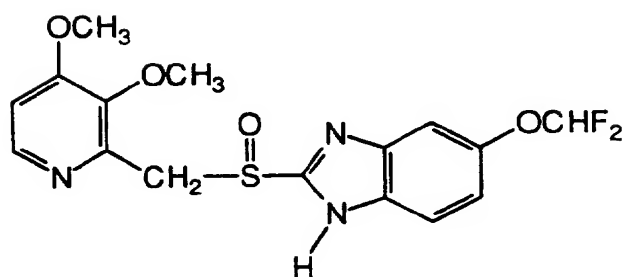


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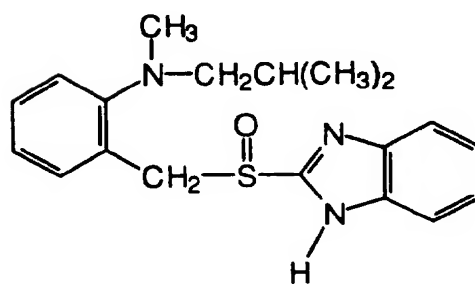




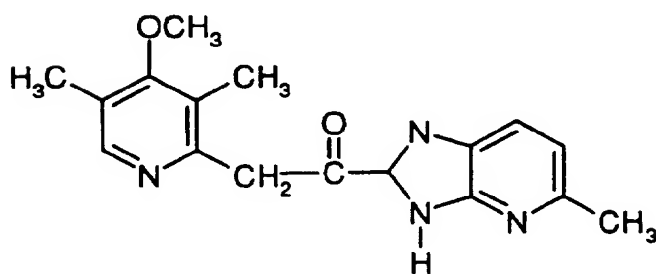
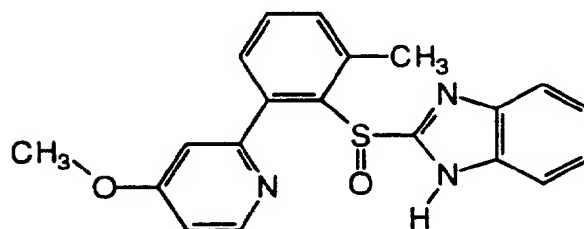
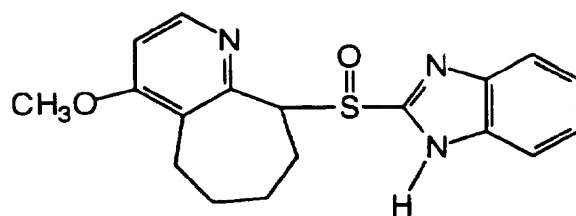
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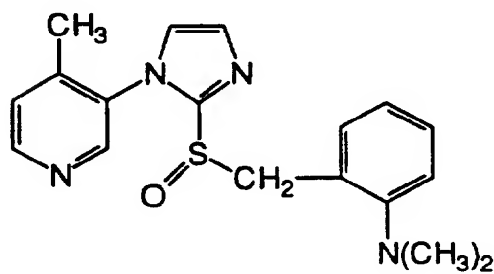
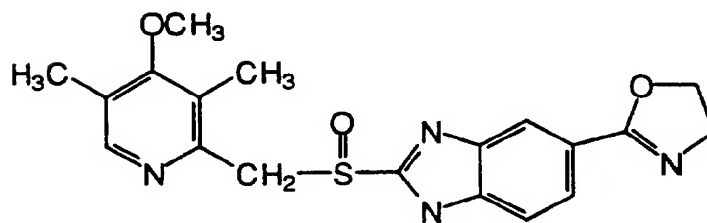
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4. A tableted effervescent dosage form according to claim 1, wherein the proton pump inhibitor is omeprazole, an alkaline salt thereof, or S-omeprazole or an alkaline salt thereof.
5. A tableted effervescent dosage form according to claim 1, wherein the acid resistance of the enteric coating layered units is in coherence with the requirements on enteric coated articles defined in the United States Pharmacopeia USP.
6. A tableted effervescent dosage form according to claim 1, wherein the acid resistance of the enteric coating layered units does not decrease more than 10 % during the compression of the enteric coating layered units into the tableted multiple unit effervescent dosage form.
7. A tableted effervescent dosage form according to claim 1, wherein the enteric coating layer of the individual units comprises a plasticized enteric coating material.
8. A tableted effervescent dosage form according to claim 7, wherein the enteric coating layer of the individual units have been prepared from water-based polymer systems.
9. A tableted effervescent dosage form according to claim 1, wherein the enteric coating layer of the individual units has a thickness of at least 10 μ m.
10. A tableted effervescent dosage form according to claim 1, wherein each individual of the enteric coating layered units are further coated with an over-coat comprising filmforming agents and optionally pharmaceutically acceptable excipients.
11. A tableted effervescent dosage form according to claim 1, wherein the effervescent tablet constituents are a carbon dioxide source and a solid acidic compound and optionally other tablet excipients.

12. A tableted effervescent dosage form according to claim 1, wherein the effervescent tablet constituents are sodium carbonate and bicarbonate, citric acid and optionally other tablet excipients.
- 5 13. A tableted effervescent dosage form according to claim 1, wherein a separating layer is optionally applied in between the core material and the enteric coating layer, characterized in that the separating layer(s) comprises polymeric, filmforming compounds or tablet excipients which are soluble, or insoluble but disintegrating in water, and optionally pH-buffering, alkaline compounds.
- 10 14. A tableted effervescent dosage form according to claim 1, wherein the proton pump inhibitor is optionally mixed with excipients and alkaline reacting material and spray layered onto inert seeds.
- 15 15. A tableted effervescent dosage form according to claim 14, wherein the inert seeds have a size of 0.1 - 2 mm.
16. A tableted effervescent dosage form according to claim 14, wherein the inert seeds are soluble sugar seeds.
- 20 17. A tableted effervescent dosage form according to claim 1, wherein the proton pump inhibitor is mixed with excipients and optionally alkaline reacting material and extruded into homogenous cores.
- 25 18. A process for the manufacture of a tableted multiple unit effervescent dosage form comprising mixing effervescent tablet constituents and enteric coating layered units of a core material comprising an acid susceptible proton pump inhibitor optionally mixed with alkaline reacting compounds, and said core material is optionally covered with one or more separating layer(s) and further covered with one or more enteric coating layer(s), whereafter
- 30 the enteric coating layered units are compressed together with the effervescent tablet constituents into a tablet, whereby the enteric coating layer(s) has mechanical properties

such that the compression of the enteric coated units with the effervescent tablet constituents into the tableted dosage form does not significantly affect the acid resistance of the enteric coating layered units.

- 5 19. A process according to claim 18, wherein the enteric coating layered units are further coated with an over-coat before compression of the units together with the effervescent tablet constituents into the tableted dosage form.

- 10 20. A method for inhibiting gastric acid secretion in mammals and man by administering to a host in need thereof a therapeutically effective dose of a tableted multiple unit effervescent dosage form according to any of claims 1 to 17.

- 15 21. A method for the treatment of gastrointestinal inflammatory diseases in mammals and man by administering to a host in need thereof a therapeutically effective dose of a tableted multiple unit effervescent dosage form according to any of claims 1 to 17.

22. Use of a tableted effervescent dosage form according to any of claims 1 - 17 for the manufacture of a medicament for inhibiting gastric acid secretion.

- 20 23. Use of a tableted effervescent dosage form according to any of claims 1 - 17 for the manufacture of a medicament for treating gastrointestinal inflammatory diseases.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/01738

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/46, A61K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE, WPI, WPIL, CLAIMS, CAPLUS, USFULLTEXT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4289751 A (J.J. WINDHEUSER), 15 Sept 1981 (15.09.81), column 2, line 9 - line 43; column 3, line 19 - line 55, claims --	1-23
A	WO 9421239 A1 (CIMA LABS, INC.), 29 Sept 1994 (29.09.94), page 6, line 20 - page 7, line 16, claims --	1-23
A	EP 0233853 A1 (LABORATORIES SMITH KLINE & FRENCH), 26 August 1987 (26.08.87) -- -----	1-23

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search

9 April 1997

Date of mailing of the international search report

22 -04- 1997

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/01738

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 20-21
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Claims 20-21 are directed to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/SE 96/01738

Patent document cited in search report			Publication date	Patent family member(s)	Publication date
US	4289751	A	15/09/81	NONE	
WO	9421239	A1	29/09/94	AU 6447294 A EP 0752852 A US 5503846 A	11/10/94 15/01/97 02/04/96
EP	0233853	A1	26/08/87	SE 0233853 T3 AU 599071 B AU 6789987 A BG 50924 A CA 1299583 A CN 1032841 B EG 18194 A FI 90941 C FR 2593065 A,B IE 59652 B JP 8175976 A JP 62215536 A KR 9502883 B NO 173972 C OA 8464 A SU 1605913 A US 4824664 A	12/07/90 23/07/87 15/12/92 28/04/92 25/09/96 30/11/94 25/04/94 24/07/87 09/03/94 09/07/96 22/09/87 28/03/95 02/03/94 29/07/88 07/11/90 25/04/89



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 45/06, 31/44, 31/19, 31/54, 9/26, 9/54	A1	(11) International Publication Number: WO 97/25064 (43) International Publication Date: 17 July 1997 (17.07.97)
(21) International Application Number: PCT/SE96/01735 (22) International Filing Date: 20 December 1996 (20.12.96) (30) Priority Data: 9600070-8 8 January 1996 (08.01.96) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): DEPUI, Helene [FR/SE]; Wrangelsgatan 7B, S-416 62 Göteborg (SE). LUNDBERG, Per, Johan [SE/SE]; Torsgatan 6, S-431 38 Mölndal (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: ORAL PHARMACEUTICAL DOSAGE FORMS COMPRISING A PROTON PUMP INHIBITOR AND A NSAID		
(57) Abstract <p>An oral pharmaceutical dosage form comprising an acid susceptible proton pump inhibitor and one or more NSAIDs in a fixed formulation, wherein the proton pump inhibitor is protected by an enteric coating layer. The fixed formulation is in the form of an enteric coating layered tablet, a capsule or a multiple unit tableted dosage form. The multiple unit dosage forms are most preferred. The new fixed formulation is especially useful in the treatment of gastrointestinal side-effects associated with NSAID treatment.</p> <div data-bbox="911 1150 1455 1423" data-label="Image"> </div>		

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ORAL PHARMACEUTICAL DOSAGE FORMS COMPRISING A PROTON PUMP INHIBITOR AND A NSAID

Field of the invention

5 The present invention is related to new oral pharmaceutical preparations especially for use in the treatment and prophylaxis of gastrointestinal disorders associated with the use of Non Steroidal Antiinflammatory Drugs (NSAIDs). The present preparations comprise an acid susceptible proton pump inhibitor in combination with one or more NSAID(s) in a new fixed unit dosage form, especially a tableted dosage form . Furthermore, the present
10 invention refers to a method for the manufacture of such preparations and the use of such preparations in medicine.

BACKGROUND OF THE INVENTION

15 NSAIDs including acetyl salicylic acid are among the most commonly prescribed and used drugs world-wide. Despite the therapeutic benefits of NSAIDs, their use is frequently limited by an increased risk of gastrointestinal side-effects, mainly upper gastrointestinal side-effects like peptic ulceration and dyspeptic symptoms.

20 The relative risk of developing a gastric ulcer during NSAID treatment is increased by a factor 40-50, and the relative risk of developing a duodenal ulcer is increased by a factor 8-10 (McCarty DM. Gastroenterology 1989;96:662). The relative risk of developing an ulcer complication like bleeding and perforation of the stomach is increased by a factor 1.5-5 (Hawkey C. BMJ 1990;300:278). Further, dyspeptic symptoms are experienced in 30-60%
25 of those on NSAID treatment (Larkai EN.AmJGas 1987;82:1153).

In the UK, NSAIDs account for 25% of all reports of adverse drug reactions received by the authorities, and the corresponding figure is 21% in USA. Therefore, therapies which avoid gastrointestinal side-effect caused by NSAIDs is requested.

Attempts to modify the NSAID structure in order to prevent such side-effects have so far been less successful. The most promising solution to the problem of healing and preventing NSAID associated upper gastrointestinal problems like ulcers and dyspeptic symptoms in patients with a need for continuous NSAID treatment is to combine the NSAID treatment with an anti-ulcer drug approved for the healing and/or prophylaxis of NSAID associated gastrointestinal side-effects such as prostaglandin analogues, H₂-receptor antagonists or proton pump inhibitors.

Established risk factors for developing NSAID associated upper gastrointestinal side-effects and complications are for instance high age, previous peptic ulcer and/or bleeding, high dose of NSAID, co-therapy with steroids, and co-therapy with anticoagulants. This means, that for example fragile and elderly patients tolerating a complication like bleeding or perforation badly, should receive prophylactic treatment in connection with their NSAID treatment.

NSAIDs are mainly used for the treatment of chronic diseases like rheumatoid arthritis and osteoarthritis, which are most often seen in the elderly population. Compliance is especially important in elderly and fragile patients, who have the highest risk of developing a life-threatening complication to NSAID treatment like bleeding or perforation. It is known that 50% of all peptic ulcer deaths occur in NSAID users and that 68% of these are >75 years old (Catford:Health Trends 1986;18:38). This is confirmed in another study concluding, that NSAID-related deaths occur primarily in those > 75 years of age (Guess. J Clin Epidemiol 1988;41:35). The importance of compliance is further supported by the finding, that a majority of peptic ulcers associated with NSAID treatment are asymptomatic until the event.

Omeprazole being a well known proton pump inhibitor has been shown to be able to prevent gastric and duodenal erosions in healthy volunteers during treatment with acetyl salicylic acid. Clinical studies have shown, that omeprazole heals gastric as well as duodenal

ulcers as fast and effectively in patients on continuous NSAID treatment as in non-NSAID users (Walan A. N Engl J Med 1989;320:69). These results have been the basis for an amendment to the dose recommendation for the use of omeprazole in healing of gastric and duodenal ulcers during continuous NSAID treatment approved by regulatory authorities in
5 UK and Sweden.

Recent studies confirm, that omeprazole significantly reduces the risk of developing gastric ulcers, duodenal ulcers and also dyspeptic symptoms in patients on continuous NSAID treatment.

10 EP 0 426 479 describes tablet compositions comprising a NSAID such as ibuprofen and a gastric acid inhibiting drug, such as cimetidin etc. No specific arrangement is taken to avoid degradation if the gastric acid inhibitor is an acid susceptible compound, such as a proton pump inhibitor.

15 In proposed therapies comprising NSAID(s) and an acid susceptible proton pump inhibitor the different active substances are administered separately. It is well known that patient compliance is a main factor in receiving a good result in medical treatments. Therefore, administration of two or even more different tablets to the patient is not convenient or
20 satisfactory to achieve the most optimal results. The present invention now provides new oral dosage forms comprising two or more different active substances combined in one fixed unit dosage form, preferably a tablet.

Some anti-ulcer drugs such as proton pump inhibitors are susceptible to
25 degradation/transformation in acid reacting and neutral media as mentioned above. In respect of the stability properties, it is obvious that the one of the active substances being a proton pump inhibitor must be protected from contact with acidic gastric juice by an enteric coating layer. There are different enteric coating layered preparations of proton pump inhibitors described in the prior art, see for example US-A 4,786,505 (AB Hässle)
30 comprising omeprazole.

There are problems to produce a fixed unit dosage form comprising a rather high amount of active substance. Active substances with different physical properties combined in the same preparation give further problems. Preparation of a multiple unit tableted dosage form arises
5 specific problems when enteric coating layered pellets containing the acid susceptible proton pump inhibitor are compressed into tablets. If the enteric coating layer does not withstand the compression of the pellets into a tablet, the susceptible active substance will be destroyed upon administration by penetrating acidic gastric juice, i.e. the acid resistance of the enteric coating layer of the pellets will not be sufficient in the tablet after compression.

10

Summary of the invention

The present invention provides oral, fixed unit dosage forms, i.e. multiple unit tableted dosage forms, enteric coating layered tablets, multilayered tablets or capsules filled with
15 more than one pharmaceutically active compound. The active compounds are preferably an acid susceptible proton pump inhibitor in combination with one or more NSAIDs and wherein at least the proton pump inhibitor is protected by an enteric coated layer. These new dosage forms will simplify the regimen and improve the patient compliance.

20 Description of the Figures

Fig. 1 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor in the form of enteric coating layered pellets (1) in admixture with a fast disintegrating granulate comprising a NSAID (2). The tablet is
25 covered by an filmcoating layer (13).

Fig. 2 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor in the form of enteric coating layered pellets (1) and a NSAID in the form of cyclodextrin complex (3) included in a fast disintegrating granulate
30 (4). The tablet is covered by a filmcoating layer (13).

Fig. 3 illustrates a cross-section of a tablet with two separate layers, one layer comprises an acid susceptible proton pump inhibitor in the form of enteric coating layered pellets (1) in admixture with excipients (5) and the other layer comprises a NSAID (6) included in a gelling matrix giving extended release. The separate layers are optionally separated by a separating layer (12) and the tablet is covered by a filmcoating layer (13).

Fig. 4 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor in the form of enteric coating layered pellets (1) and a NSAID in the form of enteric coating layered pellets (7) in admixture with excipients (5). The tablet is covered by a filmcoating layer (13).

Fig. 5 illustrates a cross-section of an enteric coating layered tablet comprising an acid susceptible proton pump inhibitor (8) in admixture with one or more NSAID(s) (9) and excipients (5). The tablet is covered by an enteric coating layer (11) and optionally a separating layer (10) is layered in between the tablet core and the enteric coating layer.

Fig. 6 illustrates a tablet comprising an acid susceptible proton pump inhibitor in the form of enteric coating layered pellets (1) in admixture with a fast disintegrating granulate (4) in a tablet core, surrounded by a coating layer comprising a NSAID substance/granulation (2). The tablet is covered by a pigmented filmcoating layer (13).

Detailed description of the invention

One object of the invention is to provide an oral, multiple unit tableted dosage form comprising an anti-ulcer drug, preferably an acid susceptible proton pump inhibitor in the form of individually enteric coating layered units, together with one or more NSAIDs and tablet excipients compressed into a tablet. The enteric coating layer(s) covering the individual units of the acid susceptible proton pump inhibitor has properties such that the compression of the units into a tablet does not significantly affect the acid resistance of the

individually enteric coating layered units. Furthermore, the multiple unit tableted dosage form provides a good stability to the active substances during long-term storage.

Alternatively, the prepared tablet has separate layers, one layer that comprises the acid susceptible proton pump inhibitor in the form of compressed enteric coated layered units and another layer that comprises the NSAID(s).

The new fixed dosage form is preferably in the form of a multiple unit tableted dosage form comprising enteric coating layered units of the acid susceptible substance and the other active substance(s) in the granulated material constituting the rest of the compressed tablet, as shown in Fig. 1.

Alternatively, the different active substances may be intimately mixed with each other and compressed into a conventional tablet, which is enteric coating layered, see Fig. 5, or both active substances are in the form of enteric coating layered pellets compressed into a multiple unit tableted formulation together with preferably fast disintegrating granules of inactive excipients, as exemplified in Fig. 4.

Further alternatives are exemplified as multiple unit dosage forms wherein the proton pump inhibitor is in the form of individually enteric coating layered units and the NSAID(s) in the form of a) a complex to obtain improved bioavailability, see Fig. 2, or b) in the form of a gelling matrix resulting in a preparation with extended release of the NSAID(s), see Fig. 3. A further alternative is a multiple dosage form with the proton pump inhibitor in the form of individually enteric coating layered units compressed into a tablet and thereupon a separate layer of the NSAID(s) is applied by spray layering on the tablet. The tablet is covered by a pigmented filmcoating layer to protect the NSAID(s), see Fig. 6, because some NSAID(s) are light sensitive and require a light protecting layer.

In still another alternative, the different active substances are dry mixed and filled into a capsule. In the latter preparation the acid susceptible proton pump inhibitor is in the form of

enteric coating layered units and the NSAID(s) is/are in the form of granules or alternatively in the form of modified release formulated units such as enteric coating layered units or units layered with a controlled release layer.

- 5 The NSAID(s) may be formulated in instant release, sustained release or extended release formulations. Alternatively, the components may be formulated in an effervescent formulation. Furthermore, as some NSAID(s) are light sensitive the formulation is preferably light protected by a pigmented tablet filmcoating layer, as exemplified in Fig. 6, or by including a pigment in one of the coating layers to be applied on the tableted dosage
10 form.

A further object of the invention is to provide a dosage form which is divisible, such as divisible tablets.

- 15 Still a further object of the invention is to provide a multiple unit tableted dosage form, which is divisible and easy to handle. Some of the multiple unit tableted dosage forms may be dispersed in a slightly acidic aqueous liquid and can be given to patients with swallowing disorders and in pediatrics. Such a suspension of dispersed units/pellets of appropriate size can be used for oral administration and also for feeding through a naso-gastric tube.

20

The different active components used in the present dosage forms are defined below.

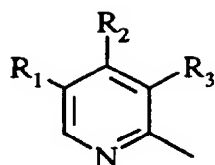
Active substances

- 25 The anti-ulcer drug is preferably an acid susceptible proton pump inhibitor. Such proton pump inhibitors are for example compounds of the general formula I



wherein

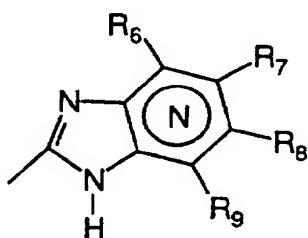
Het₁ is



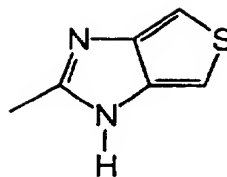
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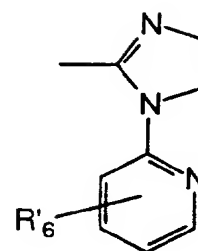
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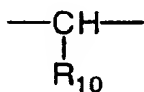
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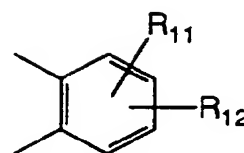
or



X =



or



wherein

10

N in the benzimidazole moiety means that one of the carbon atoms substituted by R₆-R₉ optionally may be exchanged for a nitrogen atom without any substituents;

15 R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R₄ and R₅ are the same or different and selected from hydrogen, alkyl and aralkyl;

20 R'₆ is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

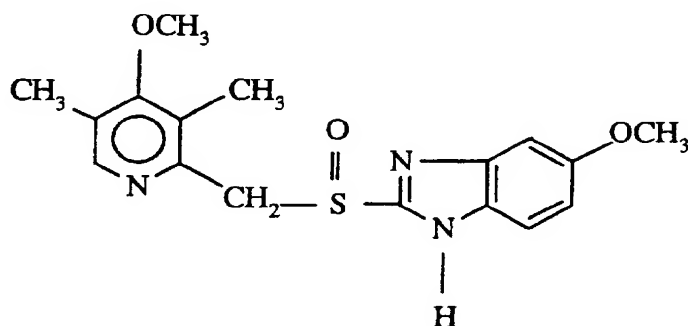
R₆-R₉ are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxy carbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R₆-R₉ form ring structures which may be further substituted;

5 R₁₀ is hydrogen or forms an alkylene chain together with R₃ and

R₁₁ and R₁₂ are the same or different and selected from hydrogen, halogen or alkyl, alkyl groups, alkoxy groups and moieties thereof, they may be branched or straight C₁ - C₉ - chains or comprise cyclic alkyl groups, such as cycloalkyl-alkyl.

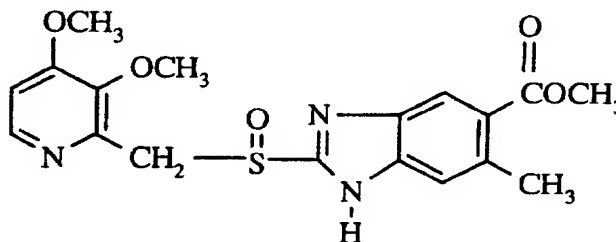
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Examples of proton pump inhibitors according to formula I are

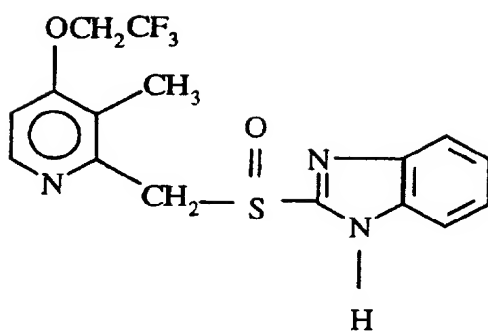
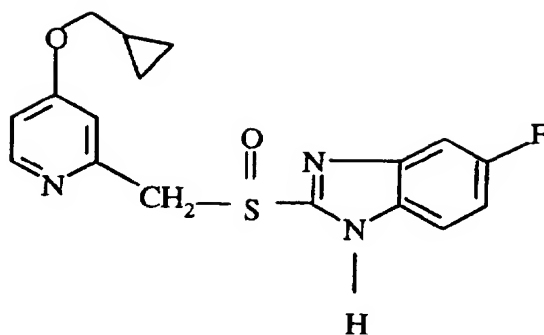


Omeprazole

15

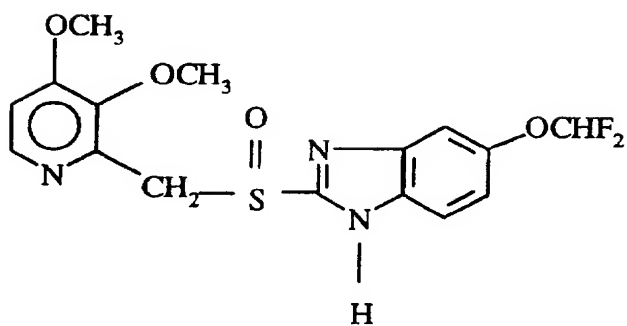


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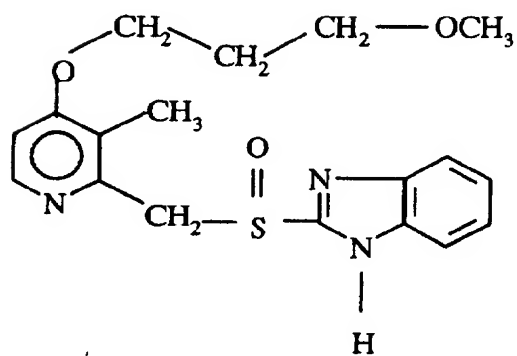


Lansoprazole

5



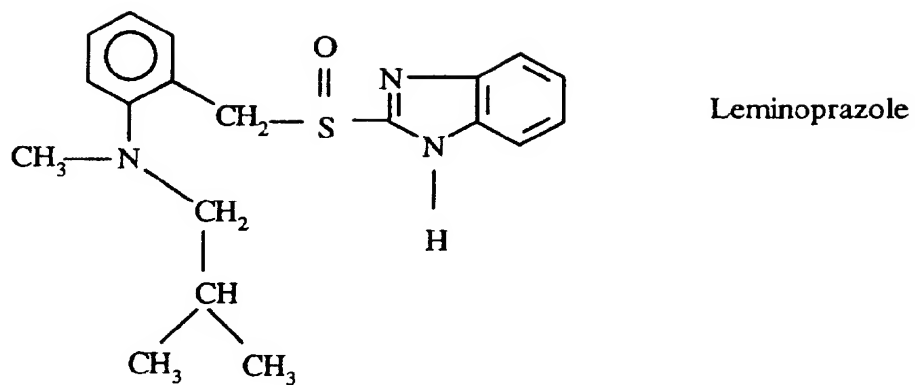
Pantoprazole



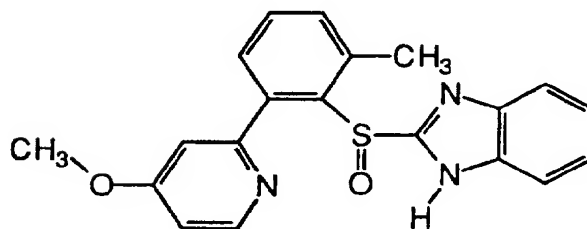
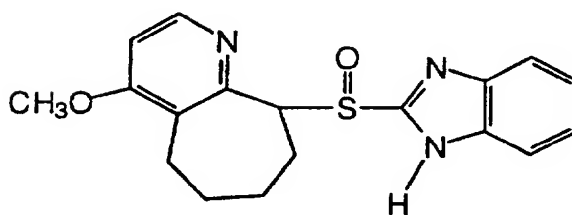
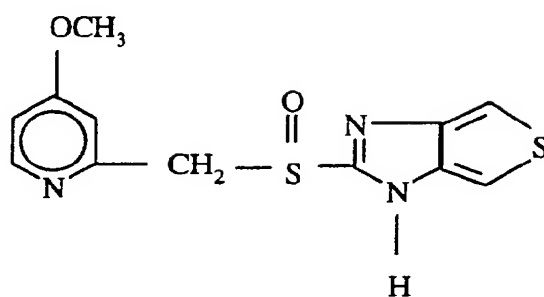
Pariprazole

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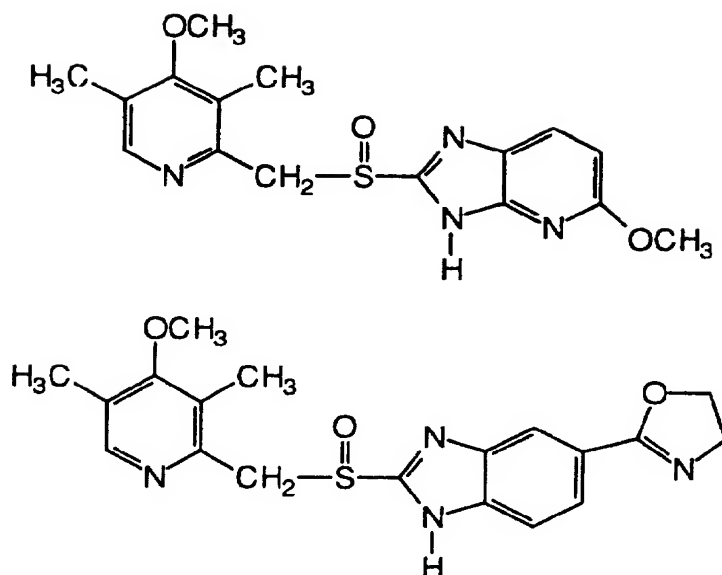
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5



10



The acid susceptible proton pump inhibitors used in the dosage forms of the invention may be used in their neutral form or in the form of an alkaline salt, such as for instance the Mg^{2+} , Ca^{2+} , Na^+ , K^+ or Li^+ salts, preferably the Mg^{2+} salts. Further where applicable, the compounds listed above may be used in racemic form or in the form of the substantially pure enantiomer thereof, or alkaline salts of the single enantiomers.

Suitable proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO90/06925, WO91/19711, WO91/19712, and further especially suitable compounds are described in WO95/01977 and WO94/27988.

A wide variety of NSAIDs may be used in combination with a suitable proton pump inhibitor and optional pharmaceutically acceptable excipients in the fixed unit dosage form according to the present invention. Such NSAIDs include for example propionic acid derivatives, oxicams, acetic acid and acetamide derivatives, salicylic acid derivatives and pyrazolidine derivatives.

Also future NSAIDs like cyclooxygenase (COX) 2 selective NSAIDs and NO-releasing NSAIDs (de Soldato P, NO-releasing NSAID:s, A new class of safer anti-inflammatory analgesic and anti-pyretic agents; The IV International meeting on side-effects of anti-inflammatory drugs August 7 - 9, 1995) may be included.

5

In the following examples of some suitable NSAIDs are listed: Acetyl salicylic acid, indometacin, diclofenac, piroxicam, tenoxicam, ibuprofen, naproxen, ketoprofen, nabumetone, ketorolac, azapropazone, mefenamic acid, tolfenamic acid, sulindac, diflunisal, tiaprofenic acid, podophyllotoxin derivatives, acemetacin, aceclofenac, droxicam, oxaprozin, floctafenine, phenylbutazone, proglumetacin, flurbiprofen, tolmetin and fenbufen.

10

The active NSAIDs could be in standard forms or used as salts, hydrates, esters etc. A combination of two or more of the above listed drugs may be used. Preferable NSAIDs for the new fixed dosage form are diclofenac, ibuprofen, naproxen and piroxicam.

15

The preferred multiple unit tableted dosage form comprising a proton pump inhibitor (in the form of a racemat, an alkaline salt or one of its single enantiomers) and one or more NSAIDs, is characterized in the following way. Individually enteric coating layered units (small beads, granules or pellets) containing the proton pump inhibitor and optionally containing alkaline reacting substances, are mixed with the NSAID(s) and conventional tablet excipients. Preferably, the NSAID(s) and tablet excipients are in the form of a granulation. The dry mixture of enteric coating layered units, NSAID granules and optional excipients are compressed into multiple unit tableted dosage forms. With the expression "individual units" is meant small beads, granules or pellets, in the following referred to as pellets of the acid susceptible proton pump inhibitor.

20

25

The compaction process (compression) for formulating the multiple unit tableted dosage form must not significantly affect the acid resistance of the enteric coating layered pellets comprising the acid susceptible proton pump inhibitor. In other words the mechanical properties, such as the flexibility and hardness as well as the thickness of the enteric coating

30

layer(s), must secure that the requirements on enteric coated articles in the United States Pharmacopeia are accomplished in that the acid resistance does not decrease more than 10% during the compression of the pellets into tablets.

- 5 The acid resistance is defined as the amount of proton pump inhibitor in the tablets or pellets after being exposed to simulated gastric fluid USP, or to 0,1 M HCl (aq) relative to that of unexposed tablets and pellets, respectively. The test is accomplished in the following way. Individual tablets or pellets are exposed to simulated gastric fluid of a temperature of 37°C. The tablets disintegrate rapidly and release the enteric coating layered pellets to the
10 medium. After two hours the enteric coating layered pellets are removed and analyzed for content of the proton pump inhibitor using High Performance Liquid Chromatography (HPLC).

- Further specific components which may be used in the fixed unit dosage forms of the
15 present invention are defined below.

Core material - for enteric coating layered pellets/units

- The core material for the individually enteric coating layered pellets can be constituted
20 according to different principles. Seeds layered with the proton pump inhibitor, optionally mixed with alkaline substances, can be used as the core material for the further processing.

- The seeds which are to be layered with the proton pump inhibitor can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or
25 in mixtures or water-soluble seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures. Further, the seeds may comprise the proton pump inhibitor in the form of crystals, agglomerates, compacts etc. The size of the seeds is not essential for the present invention but may vary between approximately 0.1 and 2 mm. The seeds layered with the proton pump inhibitor are produced either by powder or

solution/suspension layering using for instance granulation or spray coating layering equipment.

Before the seeds are layered, the proton pump inhibitor may be mixed with further
5 components. Such components can be binders, surfactants fillers, disintegrating agents, alkaline additives or other and/or pharmaceutically acceptable ingredients alone or in mixtures. The binders are for example polymers such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl-cellulose (HPC), carboxymethylcellulose sodium, polyvinyl pyrrolidone (PVP), or sugars, starches or other pharmaceutically acceptable substances with
10 cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic or ionic surfactants such as for instance sodium lauryl sulfate.

Alternatively, the proton pump inhibitor optionally mixed with alkaline substances and further mixed with suitable constituents can be formulated into a core material. Said core
15 material may be produced by extrusion/spheronization, balling or compression utilizing conventional process equipment. The size of the formulated core material is approximately between 0.1 and 4 mm and preferably between 0.1 and 2 mm. The manufactured core material can further be layered with additional ingredients comprising the proton pump inhibitor and/or be used for further processing.

20 The proton pump inhibitor is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and a suitable concentration of the proton pump inhibitor in the final preparation. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives
25 may be used.

Further, the proton pump inhibitor may also be mixed with an alkaline, pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminium
30 salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or

organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ or similar compounds; organic pH-
5 buffering substances such as trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

Alternatively, the aforementioned core material can be prepared by using spray drying or spray congealing technique.

10

Enteric coating layer(s)

Before applying the enteric coating layer(s) onto the core material in the form of individual pellets, the pellets may optionally be covered with one or more separating layer(s) comprising pharmaceutical excipients optionally including alkaline compounds such as pH-
15 buffering compounds. This/these separating layer(s), separate(s) the core material from the outer layers being enteric coating layer(s). This/these separating layer(s) protecting the core material of proton pump inhibitor should be water soluble or rapidly disintegrating in water.

20 The separating layer(s) can be applied to the core material by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating process. As an alternative the separating layer(s) can be applied to the core material by using powder coating technique. The materials for the separating layers are pharmaceutically acceptable compounds such as,
25 for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose sodium, water soluble salts of enteric coating polymers and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium
30 dioxide, talc and other additives may also be included into the separating layer(s).

- When the optional separating layer, is applied to the core material it may constitute a variable thickness. The maximum thickness of the separating layer(s) is normally only limited by processing conditions. The separating layer may serve as a diffusion barrier and may act as a pH-buffering zone. The pH-buffering properties of the separating layer(s) can be further strengthened by introducing into the layer(s) substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$, aluminium hydroxide/sodium bicarbonate coprecipitate or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, carbonic, citric or other suitable, weak, inorganic or organic acids; or suitable organic bases, including basic amino acids and salts thereof. Talc or other compounds may be added to increase the thickness of the layer(s) and thereby strengthen the diffusion barrier. The optionally applied separating layer(s) is not essential for the invention. However, the separating layer(s) may improve the chemical stability of the active substance and/or the physical properties of the novel multiple unit tableted dosage form.
- Alternatively, the separating layer may be formed in situ by a reaction between an enteric coating polymer layer applied on the core material and an alkaline reacting compound in the core material. Thus, the separating layer formed comprises a water soluble salt formed between the enteric coating layer polymer(s) and an alkaline reacting compound which is in the position to form a salt.
- One or more enteric coating layers are applied onto the core material or onto the core material covered with separating layer(s) by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in suitable organic solvents. As enteric coating layer polymers one or more, separately or in combination, of the following can be used, e.g. solutions or dispersions of methacrylic acid copolymers,

cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating polymer(s).

5 The enteric coating layers contain pharmaceutically acceptable plasticizers to obtain the desired mechanical properties, such as flexibility and hardness of the enteric coating layers. Such plasticizers are for instance, but not restricted to triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or other plasticizers.

10

The amount of plasticizer is optimized for each enteric coating layer formula, in relation to selected enteric coating layer polymer(s), selected plasticizer(s) and the applied amount of said polymer(s), in such a way that the mechanical properties, i.e. flexibility and hardness of the enteric coating layer(s), for instance exemplified as Vickers hardness, are adjusted so
15 that the acid resistance of the pellets covered with enteric coating layer(s) does not decrease significantly during compression of pellets into tablets. The amount of plasticizer is usually above 10 % by weight of the enteric coating layer polymer(s), preferably 15 - 50 % and more preferably 20 - 50 %. Additives such as dispersants, colorants, pigments polymers e.g. poly (ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be
20 included into the enteric coating layer(s). Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acid susceptible material. To protect the acid susceptible substance, the proton pump inhibitor, and to obtain an acceptable acid resistance of the dosage form according to the invention, the enteric coating layer(s) constitutes a thickness of approximately at least 10 μm , preferably more than 20
25 μm . The maximum thickness of the applied enteric coating is normally only limited by processing conditions and the desired dissolution profile.

The enteric coating layer may also be used for layering of the NSAID(s). Alternatively, the enteric coating layer described above may also be used for an enteric coating layer of
30 conventional tablets comprising a composition of a proton pump inhibitor and one or more

NSAIDs, optionally the prepared tablet core also is covered by one of the separating layers described above to separate the tablet core from the enteric coating layer.

Over-coating layer

5

Pellets covered with enteric coating layer(s) may further be covered with one or more over-coating layer(s). The over-coating layer(s) should be water soluble or rapidly disintegrating in water. The over-coating layer(s) can be applied to the enteric coating layered pellets by coating or layering procedures in suitable equipments such as coating pan, coating
10 granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating or layering process. The materials for over-coating layers are chosen among pharmaceutically acceptable compounds such as, for instance sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose
15 sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such for instance magnesium stearate, titanium dioxide, talc and other additives may also be included into the over-coating layer(s). Said over-coating layer may further prevent potential agglomeration of enteric coating layered pellets, further it may protect the enteric coating layer towards cracking
20 during the compaction process and enhance the tableting process. The maximum thickness of the applied over-coating layer(s) is normally limited by processing conditions and the desired dissolution profile. The over-coating layer may also be used as a tablet filmcoating layer.

25 NSAID preparation

The active substance(s) in the form of one or more NSAID substances is dry mixed with inactive excipients, wherein one or more of the excipients optionally is a disintegrant. The mixture is wet massed with a granulation liquid. The wet mass is dried preferably to a loss
30 on drying of less than 3% by weight. Thereafter the dry mass is milled to a suitable size for

- the granules, such as smaller than 4 mm, and preferably smaller than 1 mm. Suitable inactive excipients for the NSAID granulation are for instance, sodium starch glycolate, corn starch, crosslinked polyvinylpyrrolidone, low substituted hydroxypropyl cellulose, microcrystalline cellulose, mannitol and colloidal silicon dioxide anhydrous (Aerosil®) and the like. The dry mixture comprising NSAID(s) is mixed with a suitable granulation liquid comprising for instance, polyvinyl pyrrolidone, hydroxypropyl cellulose, polyethylene glycol, hydroxypropyl cellulose and optionally wetting agents, such as sodium lauryl sulphate, dissolved in purified water or a suitable alcohol or a mixture thereof.
- 10 Mechanical treatment may in some cases be used to form a complex between the NSAID(s) and a complex forming agent, such as beta-hydroxypropyl cyclodextrin like in Example 3 below. Cyclodextrin complexes of NSAID(s) are shown to have an increased bioavailability of the NSAID(s), see for instance Drug Dev. Ind. Pharm. 19(7), 843-852,(1993).
- 15 Further, the NSAID may be mixed with a gelling agent during the granulation, such as hydrophilic polymer(s). Suitable gelling hydrophilic polymers are for instance hydroxypropylmethylcellulose, polyoxyethylen (polyethylene glycol), hydroxypropylcellulose, hydroxyethylcellulose and xantan. The granules may also comprise buffering substances. See for instance Example 4 below. Some NSAIDs irritate the gastric mucosa and benefit from a protecting enteric coating layer and may be formulated as enteric coating layered pellets.
- 20

Multiple unit tablets

- 25 The enteric coating layered pellets comprising a proton pump inhibitor are mixed with the granules comprising NSAID(s) and tablet excipients. The mixture is compressed into a multiple unit tableted dosage form. The compressed tablet is optionally covered with a filmforming agent(s) to obtain a smooth surface of the tablet and further enhance the stability of the tablet during packaging and transport. Such a tablet filmcoating layer may further comprise additives such as anti-tacking agents, colorants and pigments or other
- 30

additives to obtain a tablet of good appearance and with a light-protection for light sensitive components.

5 The enteric coated pellets with or without an over-coat and the NSAID granules are mixed with tablet excipients such as fillers, binders, disintegrants, lubricants and other pharmaceutically acceptable additives and compressed into tablets. Suitable lubricants for the tableting process are for instance sodium stearyl fumarate, magnesium stearate and talc.

10 Alternatively, the NSAID(s) may be dry mixed with the enteric coating layered pellets comprising the proton pump inhibitor optionally together with inactive excipients and compressed into tablets (direct compression), or the different active substances may be formulated in different layers, optionally the NSAID(s) in the form of a layer with a controlled release.

15 Further, both the NSAID(s) and the proton pump inhibitor in the form of enteric coating layered pellets may be mixed with inactive tablet excipients and compressed into a tablet. The compressed tablet is optionally covered by a tablet filmcoating layer to obtain a tablet of good appearance.

20 As a further alternative a multiple unit tableted dosage form comprising the proton pump inhibitor is spray coating layered by a suspension or solution comprising the NSAID(s). The prepared tablet is thereafter covered by a pigmented tablet filmcoating layer.

25 The fraction of enteric coating layered pellets constitutes less than 75 % by weight of the total tablet weight and preferably less than 60 %. By increasing the amount of the granules comprising the NSAID(s) the fraction of enteric coating layered proton pump inhibitor pellets in the multiple unit dosage form may be reduced. By choosing small enteric coating layered pellets in the formulation according to the present invention, the number of pellets in each tablet can be held high which in turn makes the tablet divisible with retained dosing
30 accuracy.

Thus, the preferred multiple unit tablet formulation consists of enteric coating layered pellets containing one active substance in the form of an acid susceptible proton pump inhibitor, optionally mixed with alkaline reacting compound(s), compressed into tablet
5 together with granules containing NSAID(s) and optionally tablet excipients. The addition of an alkaline reacting material to the proton pump inhibitor is not necessary, in any sense but such a substance may further enhance the stability of the proton pump inhibitor or some of the alkaline reacting compounds may react in situ with the enteric coating material to form a separating layer. The enteric coating layer(s) is making the pellets of the dosage form
10 insoluble in acidic media, but disintegrating/dissolving in near neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, where dissolution of the proton pump inhibitor is desired. The NSAID(s) may be released in the stomach. The enteric coating layered pellets may further be covered with an overcoating layer before being formulated into the tablet and they may also contain one or more
15 separating layer(s) in between the core material and the enteric coating layer.

Process

The process for the manufacture of the dosage form represents a further aspect of the
20 invention. After formulation of the pellets by spray coating or layering of the proton pump inhibitor onto seeds, or by extrusion/spheronization or granulation, e.g. rotor granulation of homogeneous pellets, the pellets are first optionally covered with the separating layer(s) and then with the enteric coating layer(s) or a separating layer is spontaneously developed in situ between an alkaline core material and the enteric coating layer material. The coating is
25 carried out as described above and in the accompanying examples. The preparation of the granules comprising the NSAID(s) and enteric coating layered NSAID pellets are also described above and in the examples. The pharmaceutical processes can preferably be completely water-based.

The enteric coating layered pellets, with or without an over-coat, are mixed with the prepared granules, tablet excipients and other pharmaceutical acceptable additives and compressed into tablets. Alternatively, the different active substances in the form of powders may be intimately dry mixed with tablet excipients, wet massed and compressed into conventional tablets before applying an optional separating layer and an enteric coating layer. The NSAID(s) may also be incorporated in a coating layer applied onto a multiple unit dosage form comprising the proton pump inhibitor, or the NSAID(s) and proton pump inhibitor in the form of enteric coating layered pellets are mixed with inactive tablet excipients and compressed into a multiple unit tableted dosage form.

The different active substances may also be formulated into different layers, wherein the layer comprising the NSAID(s) may be in the form of a control release preparation. As a further alternative, the acid susceptible proton pump inhibitor in the form of enteric coating layered pellets may be filled in a capsule together with the NSAID(s) in the form of granules or enteric coating layered pellets, and optionally mixed with pharmaceutical excipients.

Use of the preparation

The dosage forms according to the invention are especially advantageous in the treatment of gastrointestinal side-effects caused by NSAID(s), such as in a continuous treatment with NSAID(s). The new dosage forms are administered one to several times a day, preferably once or twice daily. The typical daily dose of the active substances varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general each dosage form will comprise 0,1-200 mg of the proton pump inhibitor and 0,1 - 1 000 mg of the NSAID(s). Preferably, each dosage form will comprise 10-80 mg of the proton pump inhibitor and 10-800 mg of the NSAID(s), and more preferably 10-40 mg of proton pump inhibitor and 10-500 mg of the NSAID(s), respectively. Especially preferred combinations comprise for instance 10 mg omeprazole together with 50 mg diclofenac, 10 mg omeprazole and 250 mg naproxen, 10 mg omeprazole and 10 mg piroxicam, or 10 mg omeprazole and 400 mg ibuprofen.

The multiple unit tablet preparation may also be suitable for dispersion in an aqueous liquid with slightly acidic pH-value before being orally administered or fed through a naso-gastric tube.

5

The invention is illustrated more in detail in the following examples.

Examples

10 Example 1:

Fast disintegrating multiple unit tableted dosage form comprising magnesium omeprazole and ibuprofen.

15 Core material

Magnesium omeprazole	12.00 kg
Non-pareil cores	12.00 kg
Hydroxypropyl methylcellulose	1.8 kg
Water purified	35.4 kg

20

Separating layer

Core material (acc. to above)	23.50 kg
Hydroxypropyl cellulose	2.35 kg
Talc	4.03 kg
25 Magnesium Stearate	0.34 kg
Water purified	48.00 kg

Enteric coating layer

Pellets with sep layer (acc. to above)	29.00 kg
30 Methacrylic acid copolymer (30% suspension)	38.70 kg

Triethyl citrate	3.48 kg
Mono- and diglycerides (NF)	0.58 kg
Polysorbate 80	0.06 kg
Water purified	22.68 kg

5

Over-coating layer

Enteric coating layered pellets (acc. to above)	44.7 kg
Hydroxypropyl methylcellulose	0.58 kg
Mg-Stearate	0.017 kg
10 Water purified	11.6 kg

Tabletsmg/tablet

Over-coated pellets comprising omeprazole	47.85
Ibuprofen	400
15 Microcrystalline cellulose (MCC)	273.6
Polyvinylpyrrolidone cross-linked	100.4
Polyvinylpyrrolidone K-25	33.3
Sodium laurylsulphate	26.7
Water purified	297
20 Sodium stearyl fumarate	4.0

Suspension layering was performed in a fluid bed apparatus. Magnesium omeprazole was sprayed onto inert non-pareil cores from a water suspension containing the dissolved binder.

25 The prepared core material was coating layered with a separating layer in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethylcitrate and polysorbate was sprayed onto the pellets (layered with a separating layer) in a fluid bed apparatus. In the same type of apparatus the enteric coating layered pellets

were coated with hydroxypropyl methylcellulose/Mg-Stearate suspension. The obtained pellets were classified by sieving.

Tablet granulation liquid was made by dissolving 26.7 parts of sodium laurylsulphate and 33.3 parts of polyvinylpyrrolidone K-25 in 267 parts of purified water. 400 parts of ibuprofen, 226 parts of the MCC and 10.4 parts of the cross-linked polyvinylpyrrolidone were dry-mixed. The granulating liquid was added to the powder mixture and the mass wet-mixed. 30 parts of water was added as quantum satis.

The wet mass was dried in an oven at 60°C for approx. 6 hrs. The dried granules were milled to pass a 0.8 mm sieve.

The enteric coating layered omeprazole pellets, the milled ibuprofen granules, 47.6 parts of MCC, 4.0 parts sodium stearyl fumarate and 90 parts of crosslinked polyvinylpyrrolidone were mixed and compressed to tablets on a tableting machine equipped with 15 mm diameter punches. Hardness of the 886 mg tablets tested with a Schleuniger apparatus varied between 5.3 and 5.9 kP. Disintegration time tested in simulated gastric juice (USP, without enzymes) was 49-52 sec (n=2).

20

Example 2

Fast disintegrating multiple unit tableted dosage form comprising S-omeprazole magnesium salt and naproxen.

25

Core material

S-omeprazole magnesium	120 g
Non-pareil cores	150 g
Polysorbat 80	2.4 g
Hydroxypropyl methylcellulose	18 g

30

	Water purified	562 g
	<u>Separating layer</u>	
	Core material (acc. to above)	200 g
5	Hydroxypropyl cellulose	30 g
	Talc	51.4 g
	Magnesium Stearate	4.3 g
	Water purified	600 g
10	<u>Enteric coating layer</u>	
	Pellets with sep layer (acc. to above)	250 g
	Methacrylic acid copolymer 30% suspension	333.7 g
	Triethyl citrate	30 g
	Mono- and diglycerides (NF)	5.0 g
15	Polysorbate 80 (=Tween 80)	0.5 g
	Water purified	195.8 g
	<u>Over-coating layer</u>	
	Enteric coating layered pellets	371 g
20	Carboxymethylcellulose-sodium	5.0 g
	Water purified	191 g
	<u>Tablets</u>	<u>mg/tablet</u>
	Over-coated pellets comprising	
25	S-omeprazole Mg-salt	55
	Naproxen	250
	Microcrystalline cellulose (MCC)	150
	Hydroxypropylcellulose, low substituted	40
	Polyvinylpyrrolidone K-90	5.0
30	Water purified	250

Suspension layering was performed in a fluid bed apparatus. S-omeprazole magnesium salt was sprayed onto inert sugar seeds (non-pareil cores) from a water suspension containing the dissolved binder and polysorbat 80.

5

The prepared core material was coating layered by a separating layer in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethylcitrate and polysorbate was sprayed onto the pellets (with separating layer) in a fluid bed apparatus. In the same type of apparatus the enteric coating layered pellets were covered with carboxymethylcellulose-sodium solution. The over-coating layered pellets were classified by sieving.

5 parts of polyvinylpyrrolidone K-90 was dissolved in 150 parts of purified water to form the granulation liquid. Naproxen, MCC, and low-substituted hydroxypropyl cellulose were dry-mixed. The granulating liquid was added to the powder mixture and the mass wet-mixed. 100 parts of water was added as quantum satis.

The wet mass was dried in an oven at 60°C for approx. 5-6 hrs. The dried granules were milled to pass a 1.0 mm sieve.

The enteric coating layered pellets and the milled granules were mixed and compressed to tablets on a tableting machine equipped with 18x8.5 mm punches. Average hardness for the 500 mg tablets tested (across the longest axis) with a Schleuniger apparatus was 9.4 kP. Disintegration time tested in purified water at 37 °C was 15-30 sec (n=2).

Example 3

Fast disintegrating multiple unit tableted dosage form comprising pantoprazole and piroxicam- β -hydroxypropyl-cyclodextrin.

Core material

	Pantoprazole	100 g
	Non-pareil cores	200 g
5	Hydroxypropylcellulose LF	25 g
	Water purified	607 g

Separating layer

	Core material (acc. to above)	200 g
10	Hydroxypropyl cellulose LF	20 g
	Talc	34.3 g
	Magnesium Stearate	2.9 g
	Water purified	400 g

15 Enteric coating layer

	Pellets with sep layer (acc. to above)	200 g
	Methacrylic acid copolymer, 30% suspension	333 g
	Triethyl citrate	30 g
	Mono- and diglycerides (NF)	5 g
20	Polysorbate 80	0.5 g
	Water purified	281.5 g

Tablets

		<u>mg/tablet</u>
	Pellets comprising pantoprazole	133
25	Piroxicam	20
	β -hydroxypropyl-cyclodextrin, (90%)	72
	Microcrystalline cellulose (MCC)	276
	Polyvinylpyrrolidone cross-linked	36.8
	Water purified	≤ 2

Sodium stearyl fumarate (SSF)

3.9

Suspension layering was performed in a fluid bed apparatus. Pantoprazole was sprayed onto
5 inert sugar seeds (non-pareil cores) from a water suspension containing the dissolved
binder.

The prepared core material was coating layered by a separating layer in a fluid bed
apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate.

10 The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides,
triethylcitrate and polysorbate was sprayed onto the pellets (with a separating layer) in a
fluid bed apparatus. The pellets were classified by sieving.

The piroxicam was added to β -hydroxypropyl-cyclodextrin during mechanical treatment and
15 moisturization with the water. The mass was dried in a drying oven at 50°C and then milled
to pass a 0.8 mm sieve.

The piroxicam- β -hydroxypropyl-cyclodextrin, the MCC, the cross-linked
polyvinylpyrrolidone and the SSF were dry-mixed and thereafter this mixture was mixed
20 with the pantoprazole pellets.

Compression to tablets was done on a tableting machine equipped with 18x8.5 mm
punches. Average hardness for the 577 mg tablets tested with a Schleuniger apparatus was
16.7 kP with variation between 14.8 and 18.7 kP, measurement taken along the longest
25 axis. Disintegration time tested in water was approx. 4 minutes.

The tablets were coated with a pigmented dispersion like in Ex. 7.

Example 4

Two-layered tablet dosage form with fast disintegrating part having 20 mg of lansoprazole in the form of enteric coated pellets comprised in one layer, and the other layer being an extended release part designed as a hydrophilic gel matrix comprising 250 mg of naproxen.

Lansoprazole enteric coated pelletsCore material

10	Lansoprazole	400 g
	Non-pareil cores	400 g
	Hydroxypropyl methylcellulose	80 g
	Sodium laurylsulphate	3 g
	Water purified	1360 g

15

Sub-coating

	Core material (acc. to above)	100 g
	Hydroxypropyl methylcellulos	9 g
	Polyethyleneglycol 6000	1 g
20	Talc	18 g
	Ethanol 95%	250 g
	Water purified	250 g

Enteric coating

25	Sub-coated pellets (acc. to above)	100 g
	Hydroxypropyl methylcellulose phtalate	39.9 g
	Acetyltributyl citrate	8 g
	Cetanol	2.1 g
	Ethanol 95%	162 g
30	Acetone	378 g

Suspension layering was performed in a fluid bed apparatus. Lansoprazole was sprayed onto inert non-pareil cores from a water suspension containing the dissolved binder and the wetting agent.

The prepared core material was sub-coated in a Wurster equipped fluid bed apparatus with the talc suspended in a HPMC/PEG- solution. PEG also have a function as plasticizer for the HPMC.

Enteric coating was performed in the same equipment with a solution in organic solvents of the materials forming the enteric layer.

<u>Tablets</u>	<u>mg/tablet</u>
Pellets comprising lansoprazole	94
Microcrystalline cellulose	181.8
Polyvinyl pyrrolidone cross-linked	18.2
Naproxen	250
Polyoxyethylene (mwt appr. 4000000)	200
Sodium aluminium silicate	50
L-Arginine	190
Ethanol 95% (w/v) approx.	280

Naproxen, Polyox WSR 301®, L-Arginin and sodium aluminium silicate were dry-mixed. The granulating liquid, ethanol, was added to the powder mixture and the mass wet-mixed. The wet mass was dried in an oven at 60°C for approx. 8 hrs. The dried granules were milled to pass a 1.0 mm sieve.

Tablet compression was made by first pre-compressing 690 mg of the naproxen-containing granules and then filling 281 mg of a mixture consisting of 81 mg lansoprazole pellets plus 181.8 mg of MCC and 18.2 mg of crosslinked polyvinylpyrrolidone per tablet, on top. These materials were then compressed together to give the two-layered tablets on a Diaf
5 tableting machine equipped with 9x20 mm punches. Tablet hardness tested with a Schleuniger apparatus over the longest axis was approximately 14 kP.

Naproxen dissolution was tested in phosphate buffer pH 6.8. Obtained results;

	1 hrs	14% dissolved	
10	3 hrs	34%	“
	5 hrs	58%	“
	7 hrs	79%	“
	24 hrs	102%	“

15 Example 5

Fast disintegrating multiple unit tableted dosage form comprising magnesium omeprazole and piroxicam.

20 Core material (omeprazole)

Magnesium omeprazole	5.00 kg
Non-pareil cores	10.00 kg
Hydroxypropyl methylcellulose	0.75 kg
Water purified	19.65 kg

Separating layer (omeprazole)

	Core material (acc. to above)	14.60 kg
	Hydroxypropyl cellulose	1.46 kg
	Talc	2.5 kg
5	Magnesium Stearate	0.21 kg
	Water purified	29.2 kg

Enteric coating layer (omeprazole)

	Pellets with sep layer(acc. to above)	9.00 kg
10	Methacrylic acid copolymer (30% suspension)	15.00 kg
	Triethyl citrate	1.35 kg
	Mono- and diglycerides (NF)	0.22 kg
	Polysorbate 80	0.02 kg
	Water purified	8.8 kg

15

Over-coating layer (omeprazole)

	Enteric coating layered pellets	9.0 kg
	Hydroxypropyl methylcellulose	0.18 kg
	Mg-Stearate	0.005 kg
20	Water purified	3.6 kg

Suspension layering was performed in a fluid bed apparatus. Magnesium omeprazole was sprayed onto inert sugar seeds (non-pareil cores) from a water suspension containing the dissolved binder.

25

The prepared core material was coating layered by a separating layer in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethylcitrate and polysorbate was sprayed onto the sub-coated pellets in a fluid bed apparatus. In the same type of apparatus the enteric coating layered pellets were covered

30

with hydroxypropyl methylcellulose/Mg-Stearate suspension. The over-coating layered pellets were classified by sieving.

Core material (piroxicam)

5	Piroxicam micronized	35 g
	Sugar seeds	100 g
	Hydroxypropyl methylcellulose 6 cps	25 g
	Water purified	250 g
	Ethanol 99% (w/v)	250 g

10

Enteric coating layer (piroxicam)

	Piroxicam pellets (acc. to above)	100 g
--	-----------------------------------	-------

15

were coated with a suspension of the following composition to give a product with a content of 163 mg/g;

	Hydroxypropyl methylcellulose acetatesuccinate LF	14.38 parts
	Triethyl citrate	2.87 parts
	Sodium laurylsulphate	0.43 parts
20	Talc	4.32 parts
	Water purified	183.3 parts

25

Suspension layering was performed in a fluid bed apparatus. Micronized piroxicam was sprayed onto inert non-pareil cores from a water suspension containing the dissolved binder.

The enteric coating layer consisting of hydroxypropyl methylcellulose acetatesuccinate, triethylcitrate, sodium laurylsulphate and talc was sprayed onto the piroxicam pellets in a fluid bed apparatus.

Tablets (for 1000 pcs)

pellets comprising omeprazole	95.7 g
pellets containing piroxicam	122.7 g
5 Microcrystalline cellulose (MCC)	240 g
Polyvinylpyrrolidone cross-linked (PVP-XL)	20 g
Hydroxypropylcellulose, low-substituted (L-HPC)	40 g
Sodium stearyl fumarate (SSF)	4.6 g

- 10 MCC, L-HPC and PVP-XL were mixed together until homogeneity. The two kind of enteric coating layered pellets were admixed thereafter. Finally the lubricant SSF was admixed and this mixture was compressed to tablets on a tableting machine equipped with 8.5x16 mm punches. Hardness of the 523 mg tablets tested with a Schleuniger apparatus varied between 8 and 9 kP. Disintegration time tested in water 37°C was less than 1 minute

15

The tablets were coated with a pigmented dispersion like in Example 7.

Example 6

- 20 Fast disintegrating enteric coating layered tablet comprising magnesium omeprazole and diclofenac.

Tablets (for 2000 pcs)

Omeprazole magnesium (corr. 20 mg omeprazole)	45.0 g
25 Diclofenac sodium (corr. 20 mg diclofenac)	43.2 g
Microcrystalline cellulose (MCC)	110 g
Polyvinylpyrrolidone cross-linked (PVP-XL)	50 g
Hydroxypropylcellulose, low-substituted (L-HPC)	50 g
Sodium stearyl fumarate (SSF)	8.6 g
30 Water purified	approx. 170 g

The omeprazole, diclofenac, MCC, L-HPC, 30 grams of PVP-XL and 5.6 grams of SSF were mixed and then the water was added during continuously mixing. The granulate was dried in a drying oven at 60°C for approx. 1.5 hours. The dry granulate was milled to pass
5 sieve 1.0 mm.

The milled granules were mixed with 20 grams of PVP-XL and 3.0 grams of SSF. This mixture was compressed to 153 mg tablets on a tableting machine using 7 mm diameter punches. Average tablet hardness was 7.4 kP (n=6). Disintegration time in water 37°C was
10 1 minute 20 seconds (n=1).

The tablets were coating layered with a separating layer consisting of hydroxypropyl methylcellulose (HPMC) and talc in a Wurster equipped fluidized bed.

15 Application of separating layer

	Tablets 7 mm	100.1 g
	coating dispersion;	
20	HPMC 6 cps	5.5 g
	Talc	1.15 g
	EtOH 99%(w/v)	46.7 g
	Water purified	46.7 g
25	The obtained coating layered tablets were further coating layered by an enteric coating layer in the same apparatus.	

Application of enteric coating layer

	Tablets with separating layer	100 g
5	coating dispersion;	
	Methacrylic acid copolymer as 30% suspension	26.4 g (7.92 g dry mtrl.)
	Polyethyleneglycole 400	0.9 g
	Titanium dioxide	0.83 g
	Iron oxide reddish brown	0.28 g
10	Water purified	55.1 g

The weight increase of the tablets in the enteric coating step was approx. 11 mg/tablet, corresponding to approx. 7% of the weight of charged tablets.

15 The pigments in the enteric coating layer provides protection against light.

Example 7

Fast disintegrating multiple unit tableted dosage form comprising magnesium omeprazole
20 and an inner coating layer comprising diclofenac-sodium and an outer pigmented coating layer providing light protection.

Magnesium omeprazole enteric coating layered pellets from Ex. 5.

25	<u>Tablets</u>	<u>mg/tablet</u>
	Pellets comprising omeprazole	83.3
	Microcrystalline cellulose (MCC)	181.4
	Polyvinylpyrrolidone cross-linked	3.7
	Sodium stearyl fumarate (SSF)	0.4

Pellets were prepared as in Example 5.

The MCC, the cross-linked polyvinylpyrrolidone and the omeprazole containing pellets were dry-mixed. Thereafter the SSF was admixed.

5

The mixture was compressed to tablets on a tableting machine equipped with 9 mm diameter punches. Hardness of the 269 mg tablets tested with a Schleuniger apparatus varied between 8 and 9 kP.

10 The tablets were coated in a fluidized bed with the solution below, until average tablet weight was 298 mg.

	Diclofenac-sodium	20.0 parts by weight
	HPMC 6 cps	11.4 parts by weight
15	EtOH 99%(w/v)	113.6 parts by weight
	Water purified	113.6 parts by weight

Finally these tablets were covered with pigmented suspension in the same equipment. The composition of the coating suspension was;

20

	HPMC 6 cps	10 parts by weight
	Polyethylene glycol mwt 6000	2.5 parts by weight
	TiO ₂	1.83 parts by weight
	Iron oxide yellow	0.40 parts by weight
25	EtOH 99%(w/v)	85 parts by weight
	Water purified	85 parts by weight

Obtained average tablet weight was 303 mg. Disintegration time tested in water 37°C was less than 4 minutes (n=4).

Example 8

A capsule formulation comprising magnesium omeprazole and piroxicam.

5 Capsules

Enteric coating layered omeprazole pellets

(manufacturing and composition as in Ex. 5) 95.7mg/cap

Enteric coating layered piroxicam pellets

(manufacturing and composition as in Ex. 5) 122.7mg/cap

10

Prepared pellets are filled into hard gelatine capsules, size 3. Optionally a small amount of lubricant is added before filling into capsules. The amount of omeprazole in each capsule is approx. 20 mg and the amount of piroxicam is approx. 20 mg.

15 Example 9

A capsule formulation comprising S-omeprazole magnesium salt and naproxen.

Capsules

20 Enteric coating layered pellets

(manufacturing and composition as in Ex. 2) 55.2mg/cap

Naproxen granulation

(manufacturing and composition as in Ex. 2) 445mg/cap

25 Prepared granules and enteric coating layered pellets are filled into hard gelatine capsules, size 00. Optionally a small amount of lubricant is added before filling into capsules. The amount of S-omeprazole in each capsule is approx. 10 mg and the amount of naproxen is approx. 250 mg.

Example 10:

Fast disintegrating multiple unit tableted dosage form comprising magnesium omeprazole and diclofenac-Na.

5

Core material

	Magnesium omeprazole	5 kg
	Sugar sphere seeds	10 kg
	Hydroxypropyl methylcellulose	0.75 kg
10	Water purified	19.7 kg

Separating layer

	Core material	10.2 kg
	Hydroxypropyl cellulose	1.02 kg
15	Talc	1.75 kg
	Magnesium stearate	0.146 kg
	Water purified	21.4 kg

Enteric coating layer

20	Pellets covered with separating layer	11.9 kg
	Methacrylic acid copolymer (30 % suspension)	19.8 kg
	Triethyl citrate	1.79 kg
	Mono- and diglycerides (NF)	0.297 kg
	Polysorbate 80	0.03 kg
25	Water purified	11.64 kg

Over-coating layer

	Enteric coating layered pellets	20.0 kg
	Hydroxypropyl methylcellulose	0.238 kg
30	Magnesium stearate	0.007 kg

Water purified 6.56 kg

<u>Tablets</u>	<u>mg/tablet</u>
Overcoated pellets comprising omeprazole	82.4
5 Diclofenac-Na	50.0
Microcrystalline cellulose (MCC)	261
Polyvinylpyrrolidone cross-linked	5.6
Sodium stearyl fumarate	0.56

- 10 Suspension layering was performed in a fluid bed apparatus. Magnesium omeprazole was sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder. The size of sugar sphere seeds were in the range of 0.25 to 0.35 mm.
- The prepared core material was covered with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid
- 15 copolymer, mono- and diglycerides, triethyl citrate and polysorbate was sprayed onto the pellets covered with a separating layer in a fluid bed apparatus. In a fluid bed apparatus enteric coating layered pellets were coated with a hydroxypropyl methylcellulose solution containing magnesium stearate. The over-coating layered pellets were classified by sieving.
- 20 The enteric coating layered pellets with an over-coating layer, diclofenac-Na, MCC, polyvinylpyrrolidone cross-linked and sodium stearyl fumarate were dry mixed and compressed into tablets using an excenter tableting machine equipped with 11 mm punches. The amount of omeprazole in each tablet was approx. 10 mg and the amount of diclofenac-Na was approx. 50 mg. The tablet hardness was measured to 80 N.

25

Example 11:

Fast disintegrating multiple unit tableted dosage form comprising magnesium omeprazole and piroxicam.

Core material

	Magnesium omeprazole	10.0 kg
	Sugar sphere seed	10.0 kg
	Hydroxypropyl methylcellulose	1.5 kg
5	Water purified	29.9 kg

Separating layer

	Core material	20.0 kg
	Hydroxypropyl cellulose	2.0 kg
10	Talc	3.43 kg
	Magnesium stearate	0.287 kg
	Water purified	41.0 kg

Enteric coating layer

15	Pellets covered with separating layer	24.5 kg
	Methacrylic acid copolymer (30 % suspension)	32.7 kg
	Triethyl citrate	2.94 kg
	Mono- and diglycerides (NF)	0.49 kg
	Polysorbate 80	0.049 kg
20	Water purified	19.19 kg

Over-coating layer

	Enteric coating layered pellets	37.8 kg
	Hydroxypropyl methylcellulose	0.49 kg
25	Magnesium stearate	0.0245 kg
	Water purified	11.6 kg

Tablets

		<u>mg/tablet</u>
	Overcoated pellets comprising omeprazole	94.9
30	Piroxicam	20.0

Microcrystalline cellulose (MCC)	280
Polyvinylpyrrolidone cross-linked	5.6
Sodium stearyl fumarate	0.56

- 5 Enteric coating layered pellets of magnesium omeprazole with an overcoating layer were prepared as in Example 10.

The enteric coating layered pellets with an over-coating layer, piroxicam, MCC, polyvinylpyrrolidone cross-linked and sodium stearyl fumarate were dry mixed and
 10 compressed into tablets using an excenter tableting machine equipped with 11 mm punches. The amount of omeprazole in each tablet was approx. 20 mg and the amount of piroxicam was approx. 20 mg. The tablet hardness was measured to 110 N.

Results

"Acid resistance" i.e. % left after exposure to 0.1 N HCl for 2 hrs	
	Tablets
Ex 1	95%
Ex 2	95%
Ex 3	99%
Ex 4	91%
Ex 5	92%
Ex 6	96%
Ex 7	93%
Ex 10	91%
Ex 11	91%

The best mode to practice the present invention is according to the dosage forms of the types described in examples 5, 7 and 10.

- 5 The enteric coating layered pellets comprising a proton pump inhibitor may also be prepared as described in the following examples.

Example 12

- 10 Preparation of enteric coating layered pellets by extrusion/spheronization.

Core material

	Magnesium omeprazole	600 g
	Mannitol	1000 g
15	Microcrystalline cellulose	300 g
	Hydroxypropyl cellulose	100 g
	Sodium lauryl sulphate	6 g
	Water purified	802 g

20 Separating layer

	Core material (acc. to above)	400 g
	Hydroxypropyl methylcellulose	48 g
	Water purified	960 g

25 Enteric coating layer

	Pellets covered with separating layer (acc. to above)	200 g
	Methacrylic acid copolymer	100 g
	Triethyl citrate	30 g
	Mono- and diglycerides (NF)	5 g

Polysorbate 80	0.5 g
Water purified	309 g

Sodium lauryl sulphate is dissolved in purified water to form the granulation liquid.

- 5 Magnesium omeprazole, mannitol, microcrystalline cellulose and hydroxypropyl cellulose are dry-mixed. The granulation liquid is added to the powder mixture and the mass is wet-mixed.

- 10 The wet mass is forced through an extruder equipped with screens of size 0.5 mm. The extrudate is spheronized on a friction plate in a spheronizing apparatus. The core material is dried in a fluid bed dryer and classified. The prepared core material is covered by a separating layer in a fluid bed apparatus with a hydroxypropyl methylcellulose/water solution.

- 15 The enteric coating layer is applied to the pellets covered with separating layer from an aqueous dispersion of methacrylic acid copolymer plasticized with triethyl citrate to which a mono- and diglycerides/polysorbate dispersion has been added. The pellets are dried in a fluid bed apparatus.

20 Example 13

Preparation of enteric coating layered pellets by powder layering of sugar sphere seeds.

Core material

25 Magnesium omeprazole	1 500 g
Sugar sphere seeds	1 500 g
Hydroxypropyl methylcellulose	420 g
Aerosil®	8 g
Water purified	4 230 g

Separating layer

	Core material (acc. to above)	500 g
	Hydroxypropyl cellulose	40 g
	Talc	67 g
5	Magnesium stearate	6 g
	Water purified	800 g

Enteric coating layer

	Pellets covered with separating layer (acc. to above)	500 g
10	Methacrylic acid copolymer	200 g
	Triethyl citrate	60 g
	Water purified	392 g

15 Magnesium omeprazole, part of the hydroxypropyl methylcellulose and Aerosil® are dry-mixed forming a powder. Sugar sphere seeds (0.25-0.40 mm) are layered with the powder in a centrifugal fluidized coating granulator while spraying a hydroxypropyl methylcellulose solution (6 %, w/w).

20 The prepared core material is dried and covered by a separating layer in a centrifugal fluidized coating-granulator. A fluid bed apparatus is used for enteric coating layering.

Example 14

25 Preparation of enteric coating layered pellets with cores of silicon dioxide seeds.

Core material

	Magnesium omeprazole	8.00 kg
	Silicon dioxide	8.00 kg
	Hydroxypropyl methylcellulose	1.41 kg
30	Sodium lauryl sulphate	0.08 kg

Water purified	28.00 kg
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Separating layer

Core material (acc. to above)	10.00 kg
-------------------------------	----------

5	Hydroxypropyl methylcellulose	0.80 kg
---	-------------------------------	---------

Water purified	10.00 kg
----------------	----------

Enteric coating layer

Pellets covered with separating layer (acc. to above)	300 g
---	-------

10	Methacrylic acid copolymer	124 g
----	----------------------------	-------

Polyethylene glycol 400	25 g
-------------------------	------

Mono- and diglycerides (NF)	3 g
-----------------------------	-----

Polysorbate 80	1 g
----------------	-----

Water purified	463 g
----------------	-------

15

Suspension layering is performed in a fluid bed apparatus. Magnesium omeprazole is sprayed onto the silicon dioxide seeds from a water suspension containing the dissolved binder and a surface active ingredient.

20 The prepared core material is covered with a separating layer in a fluid bed apparatus with a hydroxypropyl methylcellulose solution. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, polyethylene glycol 400 and polysorbate is sprayed onto the pellets covered with separating layer in a fluid bed apparatus.

25 Example 15

Preparation of enteric coating layered pellets.

Enteric coating layer

30 Pellets covered with separating layer

(manufacturing and composition

as in example 12)

500 g

Methacrylic acid copolymer

250 g

Polyethylene glycol 6000

75 g

5 Mono- and diglycerides (NF)

12.5 g

Polysorbate 80

1.2 g

Water purified

490 g

Example 16

10

Preparation of enteric coating layered pellets.

Enteric coating

Pellets covered with separating layer

500 g

15 (manufacturing and composition as in example 1)

Hydroxypropyl methylcellulose phthalate

250 g

Cetanol

50 g

Ethanol (95%)

1000 g

Acetone

2500 g

20

Example 17

Preparation of enteric coating layered pellets.

25 Core material

Omeprazole

225 g

Mannitol

1425 g

Hydroxypropyl cellulose

60 g

Microcrystalline cellulose

40 g

30 Lactose anhydrous

80 g

Sodium lauryl sulphate	5 g
Disodium hydrogen phosphate dihydrate	8 g
Water purified	350 g

5 Separating layer

Core material (acc. to above)	300 g
Hydroxypropyl cellulose	30 g
Talc	51 g
Magnesium stearate	4 g

10

Enteric coating layer

Pellets covered with separating layer (acc. to above)	300 g
Methacrylic acid copolymer	140 g
Triethyl citrate	42 g
15 Mono- and diglycerides (NF)	7 g
Polysorbate 80	0.7 g

20

The dry ingredients for producing the core material are well mixed in a mixer. Addition of granulation liquid is made and the mixture is kneaded and granulated to a proper consistency. The wet mass is pressed through an extruder screen and the granules are converted into a spherical form in a spheronizer. The core material is dried in a fluid bed apparatus and classified into a suitable particle size range, e.g. 0.5 - 1.0 mm. The prepared core material is covered with a separating layer and enteric coating layered as described in previous examples.

25

Preparation of active substance.

Magnesium omeprazole used in some of the examples is produced according to the process described in WO/95/01977, the single enantiomers of omeprazole salts are prepared as

described in WO/94/27988 and omeprazole is produced according to the process disclosed in EP-A1 0005129. These documents are hereby incorporated in a whole by reference.

CLAIMS

1. An oral pharmaceutical dosage form comprising an acid susceptible proton pump inhibitor together with at least one Non Steroidal Antiinflammatory Drug (NSAID) and optionally pharmaceutically acceptable excipients, characterized in that the dosage form is in the form of a fixed unit dosage form comprising at least two pharmaceutically active components, and wherein at least the proton pump inhibitor is protected by an enteric coating layer.
2. A dosage form according to claim 1, wherein the dosage form is a tablet formulation.
3. A dosage form according to claim 1, wherein the dosage form is a capsule formulation.
4. A dosage form according to claim 1, wherein the proton pump inhibitor is protected by two layers, an enteric coating layer and a layer separating the enteric coating from the proton pump inhibitor.
5. A dosage form according to claim 1, wherein the dosage form comprises a proton pump inhibitor and one NSAID.
6. A dosage form according to claim 1, wherein the proton pump inhibitor is omeprazole, an alkaline salt thereof, one of its single enantiomer or an alkaline salt thereof.
7. A dosage form according to claim 6, wherein the proton pump inhibitor is S-omeprazole magnesium salt.
8. A dosage form according to claim 1, wherein the proton pump inhibitor is lansoprazole, or one of its single enantiomers or a pharmaceutically acceptable salt thereof.

9. A dosage form according to claim 1, wherein the proton pump inhibitor is pantoprazole, or one of its single enantiomers or a pharmaceutically acceptable salt thereof.

5 10. A dosage form according to one of claims 6 - 9, wherein the NSAID is ibuprofen, diclofenac, piroxicam or naproxen, or a pharmaceutical acceptable salt thereof.

11. A dosage form according to one of claims 6 - 9, wherein the NSAID is diclofenac or piroxicam, or pharmaceutically acceptable salt thereof.

10

12. A dosage form according to claim 1, wherein the amount of proton pump inhibitor is in the range of 10-80 mg and the amount of NSAID(s) is in the range of 10-800 mg.

13. A dosage form according to claim 1, wherein the amount of proton pump inhibitor
15 is in the range of 10-40 mg and the amount of NSAID(s) is in the range of 10-500 mg.

14. A tableted dosage form according to claim 2, wherein the tablet consists of two separate layers, one layer comprising a proton pump inhibitor and the other layer comprising one or more NSAIDs.

20

15. A tableted dosage form according to claim 2, wherein the tablet formulation is a multiple unit tableted dosage form comprising the proton pump inhibitor in the form of individually enteric coating layered pellets compressed together with NSAID comprising granules into a tablet, whereby the enteric coating layer covering the individual pellets has
25 mechanical properties such that the tableting of the pellets together with the NSAID comprising granules and optionally pharmaceutically acceptable excipients does not significantly affect the acid resistance of the individually enteric coating layered pellets.

16. A tableted dosage form according to claim 15, wherein the acid resistance of the enteric coating layered pellets is in coherence with the requirements on enteric coating layered articles defined in the United States Pharmacopeia.

5 17. A tableted dosage form according to claim 15, wherein the acid resistance of the enteric coating layered pellets does not decrease more than 10 % during the compression of the pellets into the multiple unit tableted dosage form.

18. A tableted dosage form according to claim 15, wherein the enteric coating of the
10 individual pellets comprises a plasticized enteric coating layer material.

19. A tableted dosage form according to claim 15, wherein the enteric coating layered pellets are further covered with an over-coating layer comprising pharmaceutically acceptable excipients.

15

20. A tableted dosage form according to claim 15, wherein the tablet is divisible.

21. A tableted dosage form according to claim 20, wherein the tablet is dispersible to an aqueous suspension comprising NSAID(s) and enteric coating layered pellets of a proton
20 pump inhibitor.

22. A tablet dosage form according to claim 2, wherein the tablet consists of two separate layers, one layer comprising the proton pump inhibitor in the form of enteric coating layered pellets compressed with tablet excipients into a layer, and the other layer
25 gives an extended release of the incorporated NSAID(s).

23. A tablet dosage form according to claim 22, wherein the layer comprising the NSAID(s) is a gelling matrix giving extended release.

24. A tableted dosage form according to claim 2, wherein the tablet is an enteric coating layered tablet comprising a mixture of the proton pump inhibitor and the NSAID comprising granules, optionally comprising a water soluble or in water rapidly disintegrating separating layer in between the tablet core and the enteric coating layer.

5

25. A tableted dosage form according to claim 2, wherein the tablet comprising enteric coating layered pellets of the proton pump inhibitor compressed into a tablet, which tablet is covered by a separate layer comprising the NSAID(s).

10

26. A tableted dosage form according to claim 25, wherein the tablet is covered by a pigmented tablet filmcoating layer.

15

27. A tablet dosage form according to claim 2, wherein the tablet consists of two types of enteric coating layered pellets, one type comprises the proton pump inhibitor, and the other type comprises NSAID(s), together compressed with tablet excipients into a tablet.

20

28. A tablet dosage form according to claim 2, wherein the tablet consists of enteric coating layered pellets comprising the proton pump inhibitor, and pellets comprising the NSAID(s) coating layered with an extended release film, and these coating layered pellets are compressed with tablet excipients into a tablet.

25

29. A process for the manufacture of a fixed dosage form comprising a proton pump inhibitor and one or more NSAIDs in a capsule, characterized in that the proton pump inhibitor is prepared in the form of enteric coating layered pellets and that the pellets are filled into a capsule together with prepared NSAID granules or enteric coating layered NSAID pellets, or NSAID pellets coating layered with an extended release film, optionally the mixture of pellets or granules are mixed with pharmaceutically acceptable excipients, and filled in a capsule.

30. A process for the manufacture of a fixed dosage form comprising a proton pump inhibitor and one or more NSAIDs in a multiple unit tableted dosage form, characterized in that the proton pump inhibitor is prepared in the form of enteric coating layered pellets and these pellets are mixed with prepared NSAID granules and optionally pharmaceutically acceptable tablets excipients whereafter the dry mixture is compressed into a multiple unit tablet without giving any significant change of the acid resistance of the enteric coating layer.

31. A process for the manufacture of a fixed dosage form comprising a proton pump inhibitor and one or more NSAIDs in a multiple unit tableted dosage form, characterized in that the proton pump inhibitor is prepared in the form of enteric coating layered pellets and the NSAID(s) is prepared in the form of coating layered pellets wherein the coating layer is an extended release layer or an enteric coating layer, and the prepared pellets are mixed with tablet excipients and compressed into a tablet.

32. A process for the manufacture of a fixed dosage form comprising a proton pump inhibitor and one or more NSAID(s) in an enteric coating layered tablet characterized in that the proton pump inhibitor is admixed with the NSAID(s) and pharmaceutically acceptable excipients whereafter the mixture is compressed into a tablet, and the tablet is covered with an enteric coating layer and optionally covered with a separating layer before the enteric coating layer is applied.

33. A method for the treatment of gastrointestinal side-effects associated with NSAID treatment in mammals and man by administering to a host in need thereof a therapeutically effective dose of a multiple unit tableted dosage form according to any of claims 1 to 28.

34. A method according to claim 33, wherein the disorder is an upper gastrointestinal disorder associated with NSAID treatment.

35. Use of a dosage form according to any of claims 1 to 28 for the manufacture of a medicament for treatment or prevention of gastro intestinal side-effects associated with NSAID(s) treatment disorders.
- 5 36. Use according to claim 35 wherein the disorder is an upper gastrointestinal disorder associated with NSAID treatment.

1 / 2

Fig. 1

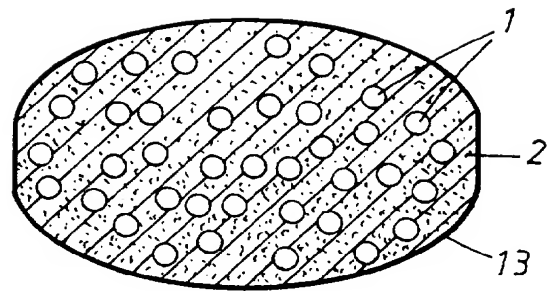


Fig. 2

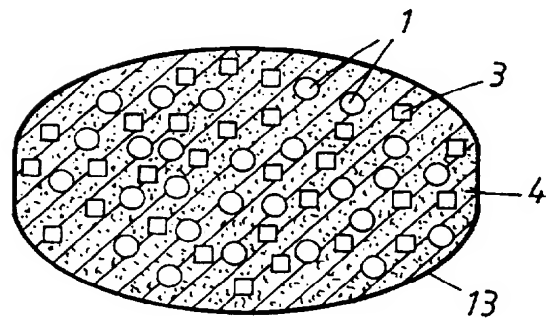
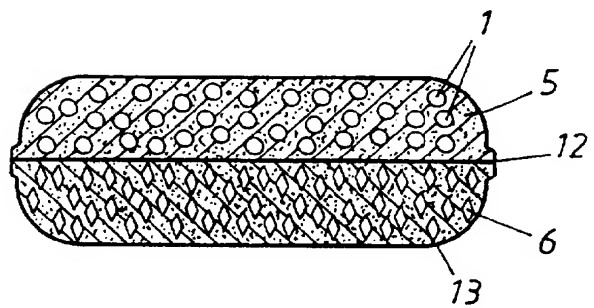


Fig. 3



2 / 2

Fig. 4

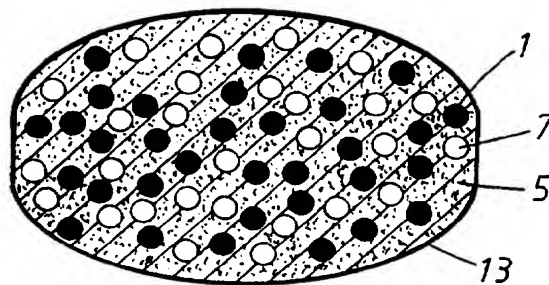


Fig. 5

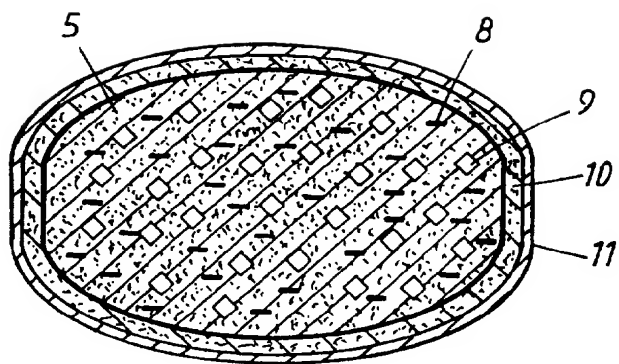
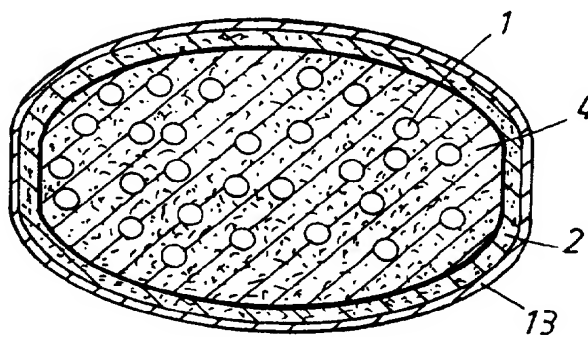


Fig. 6



INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/01735

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 45/06, A61K 31/44, A61K 31/19, A61K 31/54, A61K 9/26, A61K 9/54
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, US FULLTEXT, WPI, WPIL, CLAIMS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0426479 A1 (MCNEIL-PPC, INC.), 8 May 1991 (08.05.91) --	1-36
A	STN International, File CAPLUS, CAPLUS accession no. 1992:187668, Scheiman, James M. "Pathogenesis of gastroduodenal injury due to nonsteroidal antiinflammatory drugs", Semin. Arthritis Rheum. (1992), 21(4), 201-10 --	1-36
A	EP 0247983 A2 (AKTIEBOLAGET HÄSSLE), 2 December 1987 (02.12.87), page 4, line 25 - page 5, line 2; page 8, line 22 - line 32 --	12-36

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search

9 April 1997

Date of mailing of the international search report

22.04.97

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/01735

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0365947 A1 (PHARMACIA AB), 2 May 1990 (02.05.90), page 3, line 41 - line 46; page 4, line 42 - line 57 -- -----	12-36

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/01735

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 33-34
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Claims 33-34 are directed to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

04/03/97

International application No.

PCT/SE 96/01735

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
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				AU	6568990 A	09/05/91
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INTERNATIONAL SEARCH REPORT

Information on patent family members

04/03/97

International application No.

PCT/SE 96/01735

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				ES 2055775 T	01/09/94
				HK 123394 A	18/11/94
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 45/06, 31/44, 31/445, 9/20, 9/26, 9/48	A1	(11) International Publication Number: WO 97/25065 (43) International Publication Date: 17 July 1997 (17.07.97)
(21) International Application Number: PCT/SE96/01736 (22) International Filing Date: 20 December 1996 (20.12.96) (30) Priority Data: 9600072-4 8 January 1996 (08.01.96) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): DEPU, Helene [FR/SE]; Wrangelsgatan 7B, S-416 62 Göteborg (SE). HALLGREN, Agneta [SE/SE]; Hökegårdsgatan 2C, S-431 38 Mölndal (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: ORAL PHARMACEUTICAL DOSAGE FORMS COMPRISING A PROTON PUMP INHIBITOR AND A PROKINETIC AGENT		
(57) Abstract <p>An oral pharmaceutical dosage form comprising a proton pump inhibitor and one or more prokinetic agents in a fixed formulation, wherein the proton pump inhibitor is protected by an enteric coating layer. The fixed formulation is in the form of multilayered tablets, capsules or multiple unit tableted dosage forms. The multiple unit dosage forms are most preferred. The new fixed formulation is especially useful in the treatment of disorders associated with gastro oesophageal reflux diseases.</p> <div data-bbox="938 1157 1437 1480" data-label="Image"> <p>The diagram shows a cross-section of an oval-shaped tablet. It is divided into several layers. Layer 1 is the outermost layer, indicated by a line pointing to the top edge. Layer 2 is the middle layer, indicated by a line pointing to the center. Layer 7 is the innermost layer, indicated by a line pointing to the bottom edge. The tablet contains numerous small circles, representing individual dosage units, distributed throughout the layers.</p> </div>		

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GA	Gabon			VN	Viet Nam

ORAL PHARMACEUTICAL DOSAGE FORMS COMPRISING A PROTON PUMP INHIBITOR AND A PROKINETIC AGENT

Field of the invention

5 The present invention is related to new oral pharmaceutical preparations especially for use in the prevention and treatment of disorders associated with gastro oesophageal reflux. The present preparations comprise a gastric acid suppressing agent, such as a proton pump inhibitor, in combination with one or more prokinetic agents in a new fixed unit dosage form, especially a tablet. Furthermore, the present invention refers to a method for the
10 manufacture of such preparations and the use of such preparations in medicine, especially in the treatment of gastro oesophageal reflux diseases and other gastrointestinal disorders.

Background of the invention

15 Gastro oesophageal reflux disease (GORD) is among the most common disorders seen by gastroenterologists and general practitioners. The wide diversity of symptoms and disease severity produced by acid reflux has led to the need for more individualized treatment strategies. Therapeutic agents effective in the treatment of GORD include gastric acid suppressing agents, such as H₂ receptor antagonists, proton pump inhibitors, other agents
20 of interest are antacids/alginates and prokinetic agents. These agents can be distinguished by their mechanisms of action, safety profile, pharmacokinetics and indications.

Antacids and alginates are still widely used. They have a short duration of action but are seen as inexpensive and safe. They do not provide a layterm symptom resolution of GORD.

25

H₂ receptor antagonists are widely prescribed for GORD. Their higher cost has been compensated by the clinical results obtained both in terms of symptom relief and healing. These advantages have been related to their mode of action, which offered more potent and longer duration of effect on gastric acidity.

Proton pump inhibitors, such as omeprazole, are rapidly taking share from H₂ receptor antagonists, particularly in reflux oesophagitis. Omeprazole is known to offer significant gain over H₂ receptor antagonists in terms of symptom resolution, healing and prevention of relapse for reflux oesophagitis.

Prokinetic agents of the first generation, e.g. bethanecol, stimulates cholinergic receptors, and of the second generation, e.g. domperidone and metoclopramide, blocks effects of endogenous dopamine in the gut. The results of double-blind placebo controlled trials in GORD patients have been conflicting. The action of the third generation of prokinetic agents, such as substituted benzamides, e.g. cisapride and mosapride derives primarily, but not exclusively, from facilitating acetylcholine release from neurones of the myenteric plexus via stimulation of 5-HT₄ receptors. The efficacy of orally administered benzamides, such as cisapride, in patients with GORD and reflux oesophagitis has been studied and a superior effect in alleviating gastro-oesophageal symptoms and healing low grade oesophagitis (non circumferential erosion) has been shown in most studies.

Patients with severe symptoms, severe mucosal damage or both are almost always treated with proton pump inhibitors for profound and long-term control of gastric acid secretion. Patients with mild symptoms and limited mucosal damage respond best to H₂-receptor antagonist, prokinetic agents or proton pump inhibitors.

A combination therapy of a prokinetic agent and a gastric acid lowering compound is rational and was shown more effective than mono therapy apart from full dose of proton pump inhibitors. Administration of cisapride and ranitidine was shown to further lower the exposure of the oesophagus to acid(s) (Inauen W et al. Gut 1993; 34: 1025 - 1031). Such a therapy was also shown to improve healing rates (de Boer WA et al. Aliment Pharmacol Ther 1994; 8: 147 - 157). WO 95/01803 describes a pharmaceutical composition of famotidine, cisapride and optionally simethicone in the treatment of gastrointestinal distress.

Maintenance therapy is often necessary to prevent recurrent symptoms and oesophagitis. Recently a combination therapy combining an acid-suppressing medication with a prokinetic (cisapride) was shown also very effective. Further, Vyneri et al (N. Engl. J Med 1995; 333: 1106 - 1110) found that omeprazole alone or in combination with cisapride was more
5 effective than ranitidine alone or cisapride alone and that omeprazole combined with cisapride was more effective than ranitidine plus cisapride. Such combination therapies might be considered for patients whose predominant symptom is regurgitation; those whose symptoms occur mainly at night; those with respiratory problems such as posterior laryngitis, asthma, chronic bronchitis, or recurrent aspiration; those with cough and
10 hoarseness related to reflux disease.

A combination therapy comprising an acid suppressing agent and a prokinetic agent is attractive, rational and effective. An acid suppressing agent plus a prokinetic agent could be an alternative to each of them separately in case of failure. However, because of the large
15 number of therapeutical tablets/pills that must be taken each day in such a therapy, the compliance of such a treatment may be a problem. It is well known that patient compliance is a main factor in receiving good results in medical treatments. Administration of two, three or even more different tablets to the patient is not convenient or satisfactory to achieve the most optimal results. The present invention now provides new oral dosage forms
20 comprising two or more different active substances combined in one fixed unit dosage form, preferably a tablet.

It is well known that some of the gastric acid suppressing agents, such as proton pump inhibitors are susceptible to degradation/transformation in acid reacting and neutral media.
25 In respect of the stability properties, it is obvious that the one of the active substances being an acid susceptible proton pump inhibitor must be protected from contact with acidic gastric juice by an enteric coating layer. There are different enteric coating layered preparations of proton pump inhibitors described in the prior art, see for example US-A 4,786,505 (AB Hässle) describing a preparation comprising omeprazole.

There are problems to produce a fixed unit dosage form comprising a rather high amount of active substance. Different active substances with differing physical properties in the same preparation give further problems. Preparation of a multiple unit tableted dosage form arises specific problems when enteric coating layered pellets containing acid susceptible proton pump inhibitors as active substance are compressed into tablets. If the enteric coating layer does not withstand the compression of the pellets into a tablet the susceptible active substance will be destroyed by penetrating acidic gastric juice, i.e. the acid resistance of the enteric coating layer of the pellets will not be sufficient in the tablet after compression.

10 Summary of the invention

The present invention provides oral, fixed unit dosage forms, i.e. a multiple unit tableted dosage forms, multilayered tablets or a capsule filled with more than one pharmaceutically active compound. The active compounds present in the dosage form are preferably an acid susceptible proton pump inhibitor which is protected by an enteric coating layer, and one or more prokinetic agents. These new dosage forms will simplify the regimen and improve the patient compliance.

Brief description of the Figures

20

Fig. 1 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor in the form of enteric coating layered pellets (1) in admixture with a prokinetic agent and pharmaceutically acceptable excipients (2). The tablet is covered by a filmcoating layer, i.e. tablet coat (7).

25

Fig. 2 illustrates a cross-section of a tablet with two separate layers, one of which comprising enteric coating layered pellets (1) in admixture with excipients (3) and the other layer comprising the prokinetic agent in admixture with pharmaceutically acceptable excipients (2). The tablet is covered by a filmcoating layer (7).

30

Fig. 3 illustrates a cross-section of an enteric coating layered tablet comprising a proton pump inhibitor in admixture with pharmaceutically acceptable excipients in the tablet core (5) surrounded by an enteric coating layer (8) and thereupon a layer of the prokinetic agent(s) in admixture with pharmaceutically acceptable excipients (6). The tablet is covered
5 by a filmcoating layer (7).

Fig. 4 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor in the form of enteric coating layered pellets (1) in admixture with excipients (3) and on the multiple unit tableted dosage form a layer
10 comprising the prokinetic agent(s) in admixture with pharmaceutically acceptable excipients (6). The tablet is covered by a filmcoating layer (7).

Detailed description of the invention

15 One object of the invention is to provide an oral, multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor in the form of individually enteric coating layered units together with one or more prokinetic agents in the form of a powder or granules compressed into a tablet. The enteric coating layer(s) covering the individual units of the proton pump inhibitor has properties such that the compression of the units into
20 a tablet does not significantly affect the acid resistance of the individually enteric coating layered units. Furthermore, the multiple unit tableted dosage form provides a good stability of the active substances during long-term storage.

The new fixed dosage form is preferably in the form of a multiple unit tableted dosage form
25 comprising enteric coating layered units of the one of the active substance which is acid susceptible and granules of the other active substance, i.e. prepared prokinetic granules as shown in Fig. 1.

The proton pump inhibitor, in the form of enteric coating layered units, may also be mixed with pharmaceutically acceptable excipients and compressed into a tablet which is then filmcoated with an aqueous suspension containing the prokinetic substance, see Fig. 4.

5 Another object of the invention is to provide a tablet preparation comprising a proton pump inhibitor in admixture with tablet excipients in a tablet core and a separate layer surrounding the tablet core, which layer comprises one or more prokinetic agent(s) presscoated onto the tablet core. The tablet core is enteric coating layered before the surrounding layer of prokinetic agents is applied. Optionally a separating layer also is applied on the tablet before
10 the enteric coating layer, see Fig. 3.

Alternatively, the prepared tablet is sectioned in separate layers, each one comprising different active substances. Preferably one layer comprises the proton pump inhibitor in the form of enteric coating layered pellets in admixture with pharmaceutically acceptable
15 excipients and another layer(s) comprises(-e) the prokinetic agent(s) in admixture with pharmaceutically acceptable excipients, respectively, see Fig. 2.

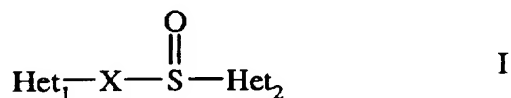
A further object of the invention is to provide a multiple unit tableted dosage form, which is divisible and easy to handle. Such a multiple unit tableted dosage form may be dispersed in
20 an aqueous liquid and can be given to patients with swallowing disorders and in pediatrics. Such a suspension of dispersed units/pellets of appropriate size can be used for oral administration and also for feeding through a naso-gastric tube.

Furthermore, the present invention provides a capsule preparation comprising the proton
25 pump inhibitor in the form of enteric coating layered pellets mixed with one or more prokinetic agents in the form of prepared granules or pellets. The new fixed unit dosage forms comprise as active substances one gastric acid suppressing agent, such as an acid susceptible proton pump inhibitor and one or more prokinetic agents. The different therapeutically active components used in the dosage forms are defined below.

The prokinetic part of the formulation may be formulated in the form of instant release, sustained release or extended release formulations. Alternatively, all the components of the formulation may be formulated in an effervescent formulation.

5 Active substances

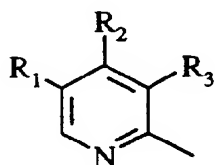
The gastric acid suppressing agent is preferably an acid susceptible proton pump inhibitor. Such proton pump inhibitors are for example compounds of the general formula I



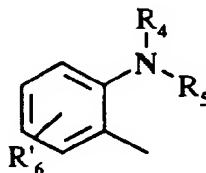
10

wherein

Het₁ is

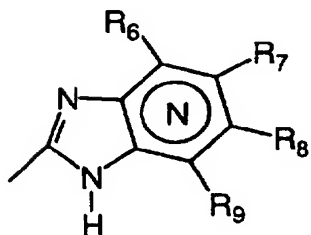


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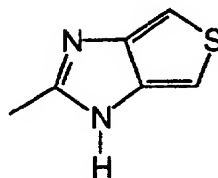


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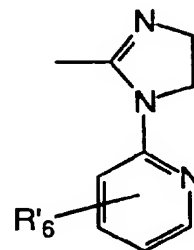
Het₂ is



or

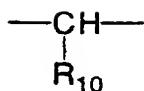


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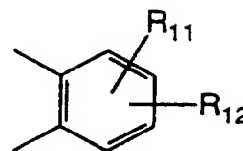


20

X =



or



wherein

- 5 N in the benzimidazole moiety means that one of the carbon atoms substituted by R₆-R₉ optionally may be exchanged for a nitrogen atom without any substituents;

R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino,
10 morpholino, halogen, phenyl and phenylalkoxy;

R₄ and R₅ are the same or different and selected from hydrogen, alkyl and aralkyl;

R₆' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

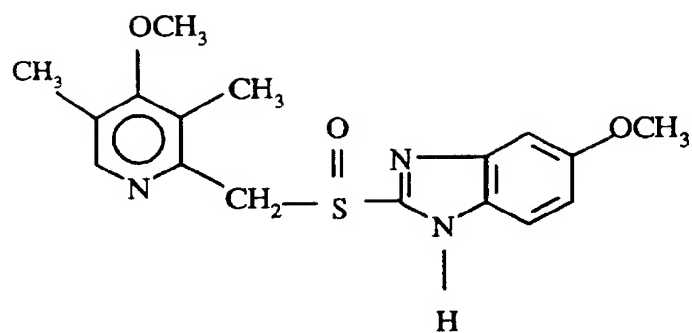
- 15 R₆-R₉ are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R₆-R₉ form ring structures which may be further substituted;

R₁₀ is hydrogen or forms an alkylene chain together with R₃ and

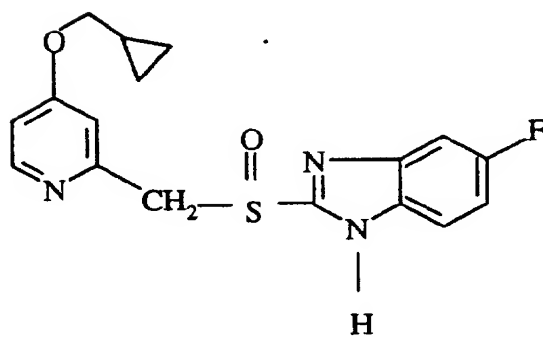
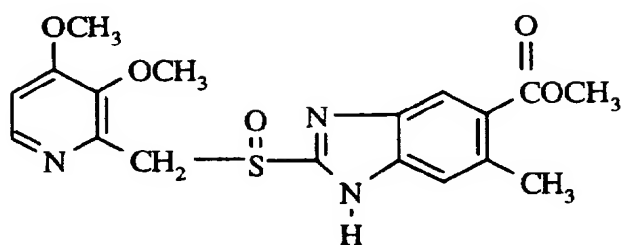
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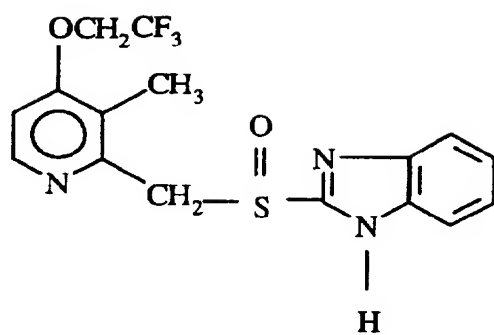
R₁₁ and R₁₂ are the same or different and selected from hydrogen, halogen or alkyl, alkyl groups, alkoxy groups and moities thereof, they may be branched or straight C₁ - C₉ - chains or comprise cyclic alkyl groups, such as cycloalkylalkyl.

- 25 Examples of proton pump inhibitors according to formula I are

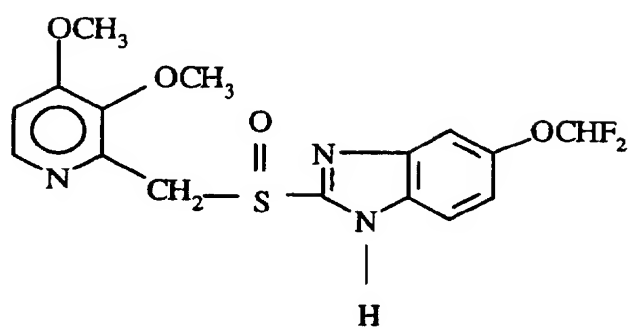


Omeprazole

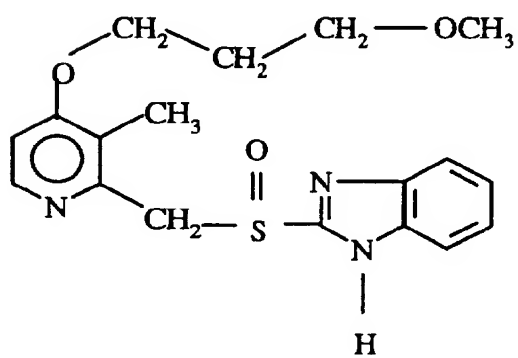




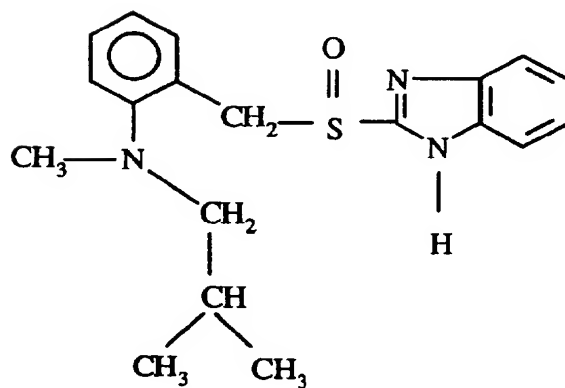
Lansoprazole



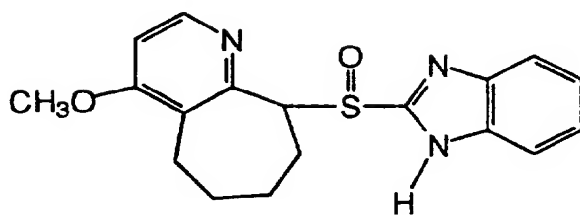
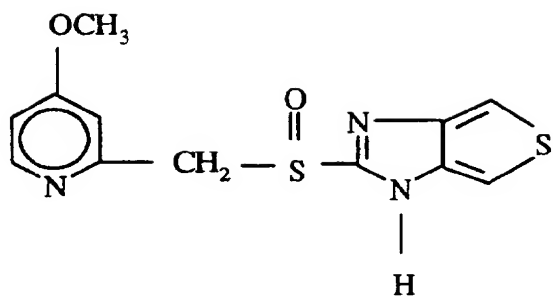
Pantoprazole



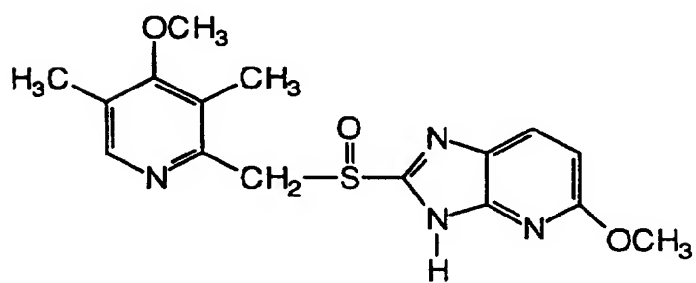
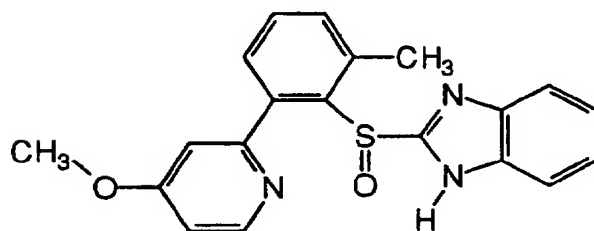
Pariaprazole

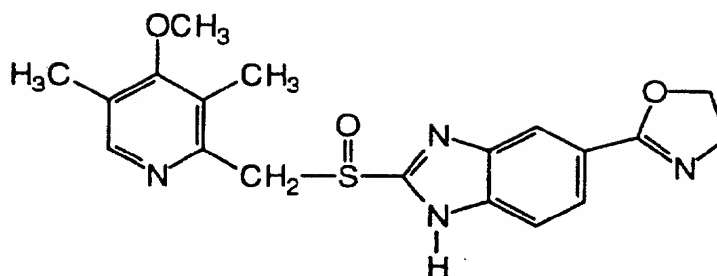


Leminoprazole



5





The proton pump inhibitors used in the dosage forms of the invention may be used in neutral form or in the form of an alkaline salt, such as for instance the Mg^{2+} , Ca^{2+} , Na^+ , K^+ or Li^+ salts, preferably the Mg^{2+} salts. Further where applicable, the compounds listed above may be used in racemic form or in the form of a substantially pure enantiomer thereof, or alkaline salts of the single enantiomers.

Suitable proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO90/06925, WO91/19711, WO91/19712, and further especially suitable compounds are described in WO95/01977 and WO94/27988.

The gastric acid suppressing agent is preferably an acid susceptible proton pump inhibitor but other gastric acid suppressing agents such as the H_2 receptor antagonists: ranitidine, cimetidine or famotidine, may be used together with a prokinetic agent in the pharmaceutical compositions according to the present invention.

A wide variety of prokinetic compounds may be used in combination with a suitable proton pump inhibitor in the fixed unit dosage form according to the present invention. Such prokinetic agents include for example cisapride, mosapride, metoclopramide, and domperidone. The active prokinetic agents could be in standard forms or used as salts, hydrates, esters etc. A combination of two or more of the above described drugs may be

used. A preferable prokinetic agent for the new fixed dosage form is mosapride or cisapride. Such suitable prokinetic agents are described in EP 0 243 959 and EP 0 076 530.

5 The preferred multiple unit tableted dosage form comprising a proton pump inhibitor in the form of a racemat, an alkaline salt or one of its single enantiomers in combination with a prokinetic compound, is characterized in the following way. Individually enteric coating layered units (small beads, granules or pellets) containing the proton pump inhibitor and optionally alkaline reacting substances, are mixed with the prokinetic compound and conventionally tablet excipients. The prokinetic compound and tablet excipients may be dry
10 mixed or wet-mixed into granules. The mixture of enteric coating layered units, prokinetic agent(s) and optionally excipients are compressed into the multiple unit tableted dosage forms. With the expression "individual units" is meant small beads, granules or pellets, in the following referred to as pellets of the proton pump inhibitor.

15 The compaction process (compression) for formulating the multiple unit tableted dosage form must not significantly affect the acid resistance of the enteric coating layered pellets. In other words the mechanical properties, such as the flexibility and hardness as well as the thickness of the enteric coating layer(s), must secure that the requirements on enteric coated articles in the United States Pharmacopeia are accomplished in that the acid resistance does
20 not decrease more than 10% during the compression of the pellets into tablets.

The acid resistance is defined as the amount of proton pump inhibitor in the tablets or pellets after being exposed to simulated gastric fluid USP, or to 0.1 M HCl (aq) relative to that of unexposed tablets and pellets, respectively. The test is accomplished in the following
25 way. Individual tablets or pellets are exposed to stimulated gastric fluid of a temperature of 37°C. The tablets disintegrate rapidly and release the enteric coating layered pellets to the medium. After two hours the enteric coating layered pellets are removed and analyzed for content of the proton pump inhibitor using High Performance Liquid Chromatography (HPLC).

Further specific components used in the fixed unit dosage forms of the present invention are defined below.

Core material - for enteric coating layered pellets comprising a proton pump inhibitor

5

The core material for the individually enteric coating layered pellets can be constituted according to different principles. Seeds layered with the proton pump inhibitor, optionally mixed with alkaline substances, can be used as the core material for the further processing.

10 The seeds which are to be layered with the proton pump inhibitor can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or in mixtures or water-soluble seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures. Further, the seeds may comprise the proton pump inhibitor in the form of crystals, agglomerates, compacts etc. The size of the seeds is not
15 essential for the present invention but may vary between approximately 0.1 and 2 mm. The seeds layered with the proton pump inhibitor are produced either by powder or solution/suspension layering using for instance granulation or spray coating layering equipment.

20 Before the seeds are layered, the proton pump inhibitor may be mixed with further components. Such components can be binders, surfactants fillers, disintegrating agents, alkaline additives or other and/or pharmaceutically acceptable ingredients alone or in mixtures. The binders are for example polymers such as hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC), carboxymethylcellulose sodium, polyvinyl
25 pyrrolidone (PVP), or sugars, starches or other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic or ionic surfactants such as for instance sodium lauryl sulfate.

Alternatively, the proton pump inhibitor optionally mixed with alkaline substances and
30 further mixed with suitable constituents can be formulated into a core material. Said core

material may be produced by extrusion/spheronization, balling or compression utilizing conventional process equipment. The size of the formulated core material is approximately between 0.1 and 4 mm and preferably between 0.1 and 2 mm. The manufactured core material can further be layered with additional ingredients comprising the proton pump inhibitor and/or be used for further processing.

The proton pump inhibitor is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and a suitable concentration of the substance in the final mixture. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives.

Further, the proton pump inhibitor may also be mixed with an alkaline, pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ or similar compounds; organic pH-buffering substances such as trihydroxymethyl-aminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

Alternatively, the aforementioned core material can be prepared by using spray drying or spray congealing technique.

Enteric coating layer(s)

Before applying the enteric coating layer(s) onto the core material in the form of individual pellets or tablets, the pellets or tablets may optionally be covered with one or more separating layer(s) comprising pharmaceutical excipients optionally including alkaline

compounds such as pH-buffering compounds. This/these separating layer(s), separate(s) the core material from the outer layers being enteric coating layer(s). The separating layer(s) protecting the core material of a proton pump inhibitor should be water soluble or rapidly disintegrating in water.

5

The separating layer(s) can be applied to the core material by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating process. As an alternative the separating layer(s) can be applied to the core material by using powder coating technique.

10 The materials for the separating layers are pharmaceutically acceptable compounds such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethyl-cellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers anti-tacking and anti-static agents, such as
15 for instance magnesium stearate, titanium dioxide, talc and other additives may also be included into the separating layer(s).

When the optional separating layer, is applied to the core material it may constitute a variable thickness. The maximum thickness of the separating layer(s) is normally only
20 limited by processing conditions. The separating layer may serve as a diffusion barrier and may act as a pH-buffering zone. The pH-buffering properties of the separating layer(s) can be further strengthened by introducing into the layer(s) substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite
25 aluminium/magnesium compounds such as, for instance $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$, aluminium hydroxide/sodium bicarbonate coprecipitate or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, carbonic, citric or other suitable, weak, inorganic or organic
30 acids; or suitable organic bases, including basic amino acids and salts thereof. Talc or other

compounds may be added to increase the thickness of the layer(s) and thereby strengthen the diffusion barrier. The optionally applied separating layer(s) is not essential for the invention. However, the separating layer(s) may improve the chemical stability of the active substance and/or the physical properties of the novel multiple unit tableted dosage form.

5

Alternatively, the separating layer may be formed in situ by a reaction between an enteric coating polymer layer applied on the core material and an alkaline reacting compound in the core material. Thus, the separating layer formed comprises a salt formed between the enteric coating layer polymer(s) and an alkaline reacting compound which is in the position to form a salt.

10

One or more enteric coating layers are applied onto the core material or onto the core material covered with separating layer(s) by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in suitable organic solvents. As enteric coating layer polymers one or more, separately or in combination, of the following can be used, e.g. solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylcellulose, shellac or other suitable enteric coating polymer(s).

15

20

The enteric coating layers may contain pharmaceutically acceptable plasticizers to obtain the desired mechanical properties, such as flexibility and hardness of the enteric coating layers. Such plasticizers are for instance, but not restricted to triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or other plasticizers.

25

The amount of plasticizer is optimized for each enteric coating layer formula, in relation to selected enteric coating layer polymer(s), selected plasticizer(s) and the applied amount of said polymer(s), in such a way that the mechanical properties, i.e. flexibility and hardness of the enteric coating layer(s), for instance exemplified as Vickers hardness, are adjusted so

30

that the acid resistance of the pellets covered with enteric coating layer(s) does not decrease significantly during compression of pellets into tablets. The amount of plasticizer is usually above 10 % by weight of the enteric coating layer polymer(s), preferably 15 - 50 % and more preferably 20 - 50 %. Additives such as dispersants, colorants, pigments polymers e.g. poly (ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be included into the enteric coating layer(s). Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acid susceptible material.

To protect the acid susceptible substance, the proton pump inhibitor, and to obtain an acceptable acid resistance of the dosage form according to the invention, the enteric coating layer(s) constitutes a thickness of approximately at least 10 μm , preferably more than 20 μm . The maximum thickness of the applied enteric coating is normally limited by processing conditions and the desired dissolution profile.

Alternatively the enteric coating layer described above may be used for enteric coating of conventional tablets comprising an acid susceptible proton pump inhibitor. Said enteric coating layered tablet is thereafter presscoated with a granulation comprising the prokinetic compound.

Over-coating layer

Pellets covered with enteric coating layer(s) may further be covered with one or more over-coating layer(s). The over-coating layer(s) should be water soluble or rapidly disintegrating in water. The over-coating layer(s) can be applied to the enteric coating layered pellets by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating or layering process. The materials for over-coating layers are chosen among pharmaceutically acceptable compounds such as, for instance sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose

- sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such for instance magnesium stearate, titaniumdioxide, talc and other additives may also be included into the over-coating layer(s). Said over-coating layer may further prevent potential agglomeration of enteric coating
- 5 layered pellets, further protect the enteric coating layer towards cracking during the compaction process and enhance the tableting process. The maximum thickness of the applied over-coating layer(s) is normally limited by processing conditions and the desired dissolution profile.
- 10 The above described over-coating layer may also be used as a tablet filmcoat to obtain tablets of good appearance.

Prokinetic preparation

- 15 The active substance(s) in form of one or more prokinetic compound(s) is dry mixed with inactive excipients and the mixture is wet massed with a granulation liquid. The wet mass is dried preferably to a loss on drying of less than 3% by weight. Thereafter the dry mass is milled to a suitable size for the granules, such as smaller than 4 mm, and preferably smaller than 1 mm. Suitable inactive excipients for the prokinetic mixture are for instance lactose,
- 20 corn starch low substituted hydroxypropyl cellulose, microcrystalline cellulose, sodium starch glycolate and crosslinked polyvinyl pyrrolidone. The dry mixture comprising prokinetic compound is wet-mixed with a suitable granulation liquid comprising for instance hydroxy propyl cellulose or polyvinyl pyrrolidone dissolved in purified water or an alcohol or a mixture thereof. Alternatively, the prokinetic agent(s) are dry mixed with
- 25 pharmaceutically acceptable excipients according to above.

- As a further alternative, the prokinetic agent(s) can be applied in a separate layer onto a multiple unit tableted dosage form or surrounding the tablet comprising the proton pump inhibitor. The prokinetic agent(s) is dispersed or dissolved in an aqueous solution optionally
- 30 comprising binders for suspension layering onto the tablet.

Multiple unit tablets

The enteric coating layered pellets comprising a proton pump inhibitor are mixed with the granules comprising prokinetic compound and tablet excipients such as fillers, binders, disintegrants, lubricants and other pharmaceutically acceptable additives. The mixture is compressed into a multiple unit tableted dosage form. The compressed tablet is optionally covered with a filmforming agent(s) to obtain a smooth surface of the tablet and further enhance the stability of the tablet during packaging and transport. Such a coating layer may further comprise additives such as anti-tacking agents, colorants and pigments or other additives to obtain a tablet of good appearance.

Alternatively the enteric coated pellets may be dry mixed with the prokinetic compound and pharmaceutically acceptable tablet excipients according to above, and compressed into tablets (direct compression).

Suitable lubricants for the tableting process are for instance sodium stearyl fumarate, magnesium stearate and talc.

Further, the different active substances may be formulated into different layers, wherein the layer comprising the proton pump inhibitor is in the form of a multiple unit tableted dosage form layered with prepared prokinetic granules. The two layers may be separated by an anti-tacking layer.

As a further alternative the proton pump inhibitor is dry mixed with inactive excipients and compressed into a conventional tablet which is coating layered with an enteric coating and optionally a separating layer is applied before the enteric coating. Thereafter the enteric coated tablet is presscoated with a prokinetic preparation. The tablet core may also be formulated as a multiple unit tableted dosage form comprising the proton pump inhibitor, the tablet is spray coating layered by a suspension comprising the prokinetic agent(s).

The fraction of enteric coating layered pellets constitutes less than 75 % by weight of the total tablet weight and preferably less than 60 %. By increasing the amount of the granules comprising the prokinetic agent the fraction of enteric coating layered pellets of the proton pump inhibitor may be reduced in the multiple unit tableted dosage form. By choosing small enteric coating layered pellets in the formulation according to the present invention, the number of pellets in each tablet can be held high which in turn makes the tablet divisible with retained dosing accuracy.

Thus, the preferred multiple unit tablet formulation consists of enteric coating layered pellets containing one active substance in the form of a proton pump inhibitor, optionally admixed with alkaline reacting compound(s), compressed into tablets together with the prepared prokinetic mixture and optionally tablet excipients. The addition of an alkaline reacting material to the proton pump inhibitor is not necessary, in any sense but such a substance may further enhance the stability of the proton pump inhibitor or some of the alkaline reacting compounds may react in situ with the enteric coating material to form a separating layer. The enteric coating layer(s) is making the pellets of the dosage form insoluble in acidic media, but disintegrating/dissolving in near neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, where dissolution of the proton pump inhibitor is desired. The prokinetic agent(s) may be released in the stomach. The enteric coating layered pellets may further be covered with an overcoating layer before being formulated into the tablet and they may also contain one or more separating layer(s) optionally containing alkaline substance(s).

Process

The process for the manufacture of the dosage form represents a further aspect of the invention. After formulation of the pellets by spray coating or layering of the proton pump inhibitor onto seeds, or by extrusion/spheronization or granulation, e.g. rotor granulation of homogeneous pellets, the pellets are first optionally covered with the separating layer(s) and

then with the enteric coating layer(s) or a separating layer is spontaneously developed in situ between the alkaline core material and the enteric coating layer material. The coating is carried out as described above and in the accompanying examples. The preparation of the prokinetic mixture is also described above and in the examples. The pharmaceutical processes can preferably be completely water-based.

The enteric coating layered pellets, with or without an over-coat, are mixed with the prepared prokinetic mixture, optionally tablet excipients and other pharmaceutically acceptable additives and compressed into tablets. Alternatively, the enteric coating layered pellets may be intimately mixed with tablet excipients and precompressed and further layered with the prepared prokinetic mixture and finally compressed into a tablet. As a further alternative the proton pump inhibitor in form of the active substance may be mixed with tablet excipients and compressed into a tablet which is optionally layered with a separating layer and thereafter enteric coating layered. Said tablet is then presscoated with the prepared prokinetic mixture. Alternatively, a multiple unit tableted dosage form of the proton pump inhibitor is manufactured as describes above. The multiple unit dosage form is spray coating layered by an aqueous suspension comprising the prokinetic agent(s). The suspension may optionally comprise binders; such as hydroxypropyl methylcellulose, and an alcohol to solve the binder. The proton pump inhibitor in the form of enteric coating layered pellets may also be filled into a capsule together with the prokinetic substance in the form of a granulation optionally mixed with pharmaceutical excipients.

Use of the preparation

The dosage forms according to the invention are especially advantageous in the treatment of gastro oesophageal reflux disease and other gastrointestinal disorder. They are administered one to several times a day, preferably once or twice daily. The typical daily dose of the active substances varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general each dosage form will comprise 0.1-200 mg of the proton pump inhibitor and 0.1-100 mg of the

prokinetic compound. Preferably, each dosage form will comprise 10-80 mg of the proton pump inhibitor and 3-80 mg of the prokinetic compound, and more preferably 10-40 mg of proton pump inhibitor and 15 - 40 mg of the prokinetic compound, respectively.

- 5 The multiple unit tablet preparation is also suitable for dispersion in an aqueous liquid with slightly acidic pH-value before being orally administered or fed through a naso-gastric tube.

The invention is illustrated more in detail in the following examples.

10 **Examples**

Example 1:

Multiple unit dosage form comprising magnesium omeprazole and mosapride (batch size
15 500 tablets).

Core material

	Magnesium omeprazole	5 kg
	Sugar sphere seeds	10 kg
20	Hydroxypropyl methylcellulose	0.75 kg
	Water purified	20.7 kg

Separating layer

	Core material (acc. to above)	10.2 kg
25	Hydroxypropyl cellulose	1.02 kg
	Talc	1.75 kg
	Magnesium stearate	0.146kg
	Water purified	21.4 kg

Enteric coating layer

	Pellets covered with separating layer (acc. to above)	11.9 kg
	Methacrylic acid copolymer (30 % suspension)	19.8 kg
	Triethyl citrate	1.79 kg
5	Mono- and diglycerides (NF)	0.297kg
	Polysorbate 80	0.03 kg
	Water purified	11.64 kg

Over-coating layer

10	Enteric coating layered pellets (acc. to above)	20 kg
	Hydroxypropyl methylcellulose	0.238kg
	Magnesium stearate	0.007kg
	Water purified	6.56 kg

15 Tablets

	Prepared pellets comprising omeprazole (acc. to above)	41.2 g
	Mosapride citrate dihydrate	23.4 g
	Microcrystalline cellulose	138.1 g
	Polyvinyl pyrrolidone crosslinked	2.9 g
20	Sodium stearyl fumarate	0.29 g

Tablet coating solution (for 10 kg tablets)

	Hydroxypropyl methylcellulose	250 g
	Polyethylene glycol 6000	62.5 g
25	Titanium dioxide	62.5 g
	Water purified	2125 g
	Hydrogen pyroxide	0.75 g

Suspension layering was performed in a fluid bed apparatus. Magnesium omeprazole was sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder. The size of sugar sphere seeds were in the range of 0.25 to 0.35 mm.

5 The prepared core material was covered with a separating layer in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethyl citrate and polysorbate was sprayed onto the pellets covered with a separating layer in a fluid bed apparatus. In a fluid bed apparatus enteric coating layered pellets were coated with
10 a hydroxypropyl methylcellulose solution containing magnesium stearate. The over-coating layered pellets were classified by sieving.

The enteric coating layered pellets with an over-coating layer, mosapride citrate dihydrate, microcrystalline cellulose, polyvinyl pyrrolidone crosslinked and sodium stearyl fumarate
15 were dry mixed and compressed into tablets using an excenter tableting machine equipped with 12 mm punches. The amount of omeprazole in each tablet was approx. 10 mg and the amount of mosapride was approx. 30 mg. The tablet hardness was measured to 70-80 N.

The obtained tablets are covered with a conventional tablet filmcoating layer.

20

Example 2:

Multiple unit dosage form comprising magnesium omeprazole and mosapride (batch size 500 tablets).

25

Mosapride granulation

Mosapride citrate dihydrate	46.8 g
Lactose monohydrate	350 g
Corn starch	184 g
30 Hydroxy propyl cellulose LF	25 g

Water purified	225 g
Hydroxypropyl cellulose (L-HPC)	152 g
Magnesium stearate	7.4 g

5 Tablets

Enteric coating layered pellets with an over-coating layer (manufacturing and composition as in example 1)	41.2 g
Mosapride granulation	190 g

10 Tablet coating solution (for 10 kg tablets)

Hydroxypropyl methyl cellulose	250 g
Polyethylene glycol 6000	62.5 g
Titaniumdioxid	62.5 g
Water purified	2125 g
15 Hydrogen peroxide	0.75g

Hydroxypropyl cellulose was dissolved in purified water to form the granulation liquid. Mosapride citrate dihydrate, lactose monohydrate and corn starch were dry mixed. The granulation liquid was added to the powder mixture and the mass was wet-mixed. The wet mass was dried in a steam-oven and milled through sieve 1 mm in an oscillating mill equipment. The prepared granulation was mixed with low substituted hydroxypropyl cellulose and magnesium stearate.

The enteric coating layered pellets with an over-coat and prepared granules were mixed and compressed into tablets using an excenter tableting machine equipped with 11 mm punches. The amount of omeprazole in each tablet was approx. 10 mg and the amount of mosapride was approx. 15 mg. Tablet hardness was measured to 30 - 40 N.

The obtained tablets are covered with a conventional tablet filmcoating layer.

Example 3:

Multiple unit dosage form comprising magnesium omeprazole and mosapride (batch size 500 tablets).

5

Core material

	Magnesium omeprazole	10	kg
	Sugar sphere seeds	10	kg
	Hydroxypropyl methylcellulose	1.5	kg
10	Water purified	29.9	kg

Separating layer

	Core material (acc. to above)	20	kg
	Hydroxypropyl cellulose	2	kg
15	Talc	3.43	kg
	Magnesium stearate	0.287	kg
	Water purified	41	kg

Enteric coating layer

20	Pellets covered with separating layer (acc. to above)	24.5	kg
	Methacrylic acid copolymer (30 % suspension)	32.7	kg
	Triethyl citrate	2.94	kg
	Mono- and diglycerides (NF)	0.49	kg
	Polysorbate 80	0.049	kg
25	Water purified	19.19	kg

Over-coating layer

	Enteric coating layered pellets (acc. to above)	37.8	kg
	Hydroxypropyl methylcellulose	0.49	kg
30	Magnesium stearate	0.0245	kg

Water purified	11.6 kg
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Tablets

Prepared pellets comprising omeprazole (acc. to above)	47.45 g
5 Mosapride citrate dihydrate	23.4 g
Microcrystalline cellulose	163 g
Polyvinyl pyrrolidone crosslinked	3.3 g
Sodium stearyl fumarate	0.3 g
10 <u>Tablet coating solution (for 10 kg tablets)</u>	
Hydroxypropyl methyl cellulose	250 g
Polyethylene glycol 6000	62.5 g
Titanium dioxid	62.5 g
Water purified	2125 g
15 Hydrogen peroxide	0.75 g

The enteric coating layered pellets with an over-coating layer prepared as described in Example 1, mosapride citrate dihydrate, microcrystalline cellulose, polyvinyl pyrrolidone crosslinked and sodium stearyl fumarate were dry mixed and compressed into tablets using an excenter tableting machine equipped with 12 mm punches.

The amount of omeprazole in each tablet was approx. 20 mg and the amount of mosapride was approx. 30 mg. The tablet hardness was measured to 70 N.

The tablets are covered with a conventional tablet filmcoating layer.

Example 4:

Multiple unit dosage form comprising S-omeprazole magnesium salt and mosapride (batch size 300 tablets).

Core material

	S-omeprazole magnesium salt	120	g
	Sugar sphere seeds	150	g
	Hydroxypropyl methylcellulose	18	g
5	Polysorbate 80	2.4	g
	Water purified	562	g

Separating layer

10	Core material (acc. to above)	200	g
	Hydroxypropyl cellulose	30	g
	Talc	51.4	g
	Magnesium stearate	4.3	g
	Water purified	600	g

15

Enteric coating layer

	Pellets covered with separating layer (acc. to above)	250	g
	Methacrylic acid copolymer (30% suspension)	333.7	g
20	Triethyl citrate	30	g
	Mono- and diglycerides (NF)	5	g
	Polysorbate 80	0.5	g
	Water purified	196	g

25 Tablets

	Prepared pellets comprising (s)-omeprazole Mg-salt (acc. to above)	38.2	g
	Mosapride citrate dihydrate	14	g
	Microcrystalline cellulose	98.3	g
	Polyvinyl pyrrolidone crosslinked	2.1	g
30	Sodium stearyl fumarate	0.2	g

Tablet coating solution (for 10 kg tablets)

	Hydroxypropyl methyl cellulose	250	g
	Polyethylene glycol 6000	62.5	g
5	Titaniumdioxid	62.5	g
	Water purified	2125	g
	Hydrogen peroxide	0.75	g

10 Suspension layering was performed in a fluid bed apparatus. S-Omeprazole magnesium salt was sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder and polysorbate 80. The size of sugar sphere seedes were in the range of 0.25 to 0.35 mm.

15 The prepared core material was covered with a separating layer in a fluid bed apparatus with hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono-and diglycerides, triethyl citrate and polysorbate was sprayed onto the pellets covered with a separating layer in a fluid bed apparatus. The enteric coating layered pellets were classified by sieving.

20 The enteric coating layered pellets, mosapride citrate dihydrate, microcrystalline cellulose, polyvinyl pyrrolidone crosslinked and sodium stearyl fumarate were mixed and compressed into tablets using an excenter tableting machine equipped with 12mm punches.

The amount of S-omeprazole in each tablet was approx. 20 mg and the amount of mosapride was approx. 30 mg. The tablet hardness was measured to 65 N.

25

The tablets are covered with a conventional tablet filmcoating layer.

“Acid resistance” i.e. % left after exposure to 0.1 N HCl for 2 hrs	
	Tablets
Ex 1	97%
Ex 2	90%
Ex 3	102%
Ex 4	104%

Example 5:

5

Multiple unit dosage form comprising lanzoprazole and mosapride (batch size 500 tablets).

Core material

	Lanzoprazole	400 g
10	Sugar sphere seeds	400 g
	Hydroxypropyl methylcellulose	80 g
	Sodium laurylsulfate	3 g
	Water purified	1500 g

15 Separating layer

	Core material (acc. to above)	400 g
	Hydroxypropyl cellulose	40 g
	Talc	69 g
	Magnesium stearate	6 g
20	Water purified	800 g

Enteric coating layer

	Pellets covered with a separating layer (acc. to above)	400 g
	Methacrylic acid copolymer (30 % suspension)	667 g
	Triethyl citrate	60 g
5	Mono- and diglycerides (NF)	10 g
	Polysorbate 80	1 g
	Water purified	420 g

Tablets

10	Prepared pellets comprising lansoprazole (acc. to above)	47 g
	Mosapride citrate dihydrate	46.8 g
	Microcrystalline cellulose	261 g
	Polyvinyl pyrrolidone crosslinked	5 g
	Sodium stearyl fumarate	0.5 g

15

Tablet coating solution (for 10 kg tablets)

	Hydroxypropyl methylcellulose	250 g
	Polyethylene glycol 6000	62.5 g
	Titanium dioxid	62.5 g
20	Water purified	2125 g
	Hydrogen peroxide	0.75 g

Suspension layering was performed in a fluid bed apparatus. Lansoprazole was sprayed onto the sugar sphere seeds from a suspension containing the dissolved binder in a water solution. Pellets covered with separating layer and enteric coating layer were produced as in example 1.

The enteric coating layered pellets, mosapride citrate dihydrate, microcrystalline cellulose, polyvinyl pyrrolidone crosslinked and sodium stearyl fumarate were dry mixed and compressed into tablets using an excenter tableting machine equipped with 10 mm punches.

The amount of lansoprazole in each tablet was approx. 10 mg and the amount of mosapride was approx. 30 mg. The tablet hardness was measured to 70 N.

The tablets are covered with a conventional tablet filmcoating layer.

5

Example 6:

Magnesium omeprazole and mosapride presscoated tablets (batch size 10.000 tablets).

10 Omeprazole tablets

Mg-omeprazole	112.5 g
Mannitol	287 g
Microcrystalline cellulose	94 g
Sodium starch glycolate	30 g
15 Hydroxypropyl methylcellulose	30 g
Talc	25 g
Microcrystalline cellulose	31 g
Sodium stearyl fumarate	12.5 g
Water purified	200 g

20

Solution for separating layer (for 10 kg tablets)

Hydroxypropyl methylcellulose	300 g
Hydrogen peroxide (30%)	0.003 g
Water purified	2700 g

25

Solution for enteric coating layer (for 10 kg tablets)

Methacrylic acid copolymer dispersion (30%)	2450 g
Polyethylene glycol 400	80 g
Titanium dioxide Colour	100 g
30 Water purified	1960 g

Presscoated tablet

Mg-Omeprazole tablets	10.000 tabl
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Mosapride granulation	
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5 (manufacturing and composition as in example 2)	3800 g
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Tablet coating solution (for 10 kg tablets)

Hydroxypropyl methylcellulose	250 g
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Polyethylene glycol 6000	62.5 g
--------------------------	--------

10 Titaniumdioxid	62.5 g
-------------------	--------

Water purified	2125 g
----------------	--------

Hydrogen peroxide	0.75 g
-------------------	--------

15 Magnesium omeprazole, mannitol, microcrystalline cellulose, sodium starch glycolate and hydroxypropyl methyl cellulose are dry mixed. The powder mixture is moistened with water purified. The granulation is dried and milled through sieve 1 mm in a suitable mill. The prepared granules comprising proton pump inhibitor is mixed with talc, microcrystalline cellulose and sodium stearyl fumarate and compressed into tablets using a rotary tableting machine equipped with 5 mm punches.

20

The obtained tablets are coated layered with a separating layer and an enteric coating layer. Said tablets are then presscoated with mosapride granulation using a presscoating machine equipped with 11 mm punched.

25 The tablets are covered with a conventional tablet filmcoating layer.

Example 7:

A capsule formulation comprising magnesium omeprazole and mosapride (batch size 100 capsules).

5

Capsules

Enteric coating layered pellets with an over-coating layer (manufacturing and composition as in example 3)	9.49 g
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Mosapride granulation (manufacturing and composition as in example 2)	38 g
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10

Enteric coating layered pellets and mosapride granulation are filled into capsules, size 00. The amount of omeprazole in each capsule is approx. 20 mg and the amount of mosapride is approx. 15 mg.

15

Example 8:

Multiple unit dosage form comprising magnesium omeprazole with a tablet coating layer comprising mosapride (batch size 1 000 tablets).

20

Tablets

Enteric coating layered pellets with an overcoat (manufacturing and composition as in example 1)	82.4 g
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Microcrystalline cellulose	179.2 g
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Polyvinyl pyrrolidone crosslinked	3.7 g
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25

Sodium stearyl fumarate	0.4 g
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Mosapride coating layer suspension

Mosapride citrate dihydrate	23.4 g
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Hydroxypropyl methyl cellulose	13.4 g
--------------------------------	--------

30

Ethanol 99 %	132.5 g
Water purified	132.5 g

Tablet coating solution (for 10 kg tablets)

5 Hydroxypropyl methylcellulose	250 g
Polyethylene glycol 6000	62.5 g
Titanium dioxid	62.5 g
Water purified	2125 g
Hydrogen peroxide	0.75g

10

The enteric coating layered pellets are mixed with microcrystalline cellulose, polyvidone and sodium stearyl fumarate and compressed into tablets using an excenter tableting machine equipped with 9 mm punches. The tablets are then coated layered in a fluid bed apparatus with the suspension comprising mosapride. The amount of omeprazole in each tablet is
15 approx. 10 mg and the amount of mosapride is approx. 15 mg.

Finally the tablets are covered with a conventional tablet filmcoating layer.

20

The best mode to practise the invention is according to compositions described in Examples 1 and 4.

The enteric coating layered pellets comprising a proton pump inhibitor may also be prepared as described in the following examples.

25

Example 9:

Preparation of enteric coating layered pellets by extrusion/spheronization.

Core material

	Magnesium omeprazole	600 g
	Mannitol	1000 g
	Microcrystalline cellulose	300 g
5	Hydroxypropyl cellulose	100 g
	Sodium lauryl sulphate	6 g
	Water purified	802 g

Separating layer

10	Core material	400 g
	Hydroxypropyl methylcellulose	48 g
	Water purified	960 g

Enteric coating layer

15	Pellets covered with separating layer	200 g
	Methacrylic acid copolymer	100 g
	Triethyl citrate	30 g
	Mono- and diglycerides (NF)	5 g
	Polysorbate 80	0.5 g
20	Water purified	309 g

Sodium lauryl sulphate is dissolved in purified water to form the granulation liquid.

Magnesium omeprazole, mannitol, microcrystalline cellulose and hydroxypropyl cellulose are dry-mixed. The granulation liquid is added to the powder mixture and the mass is wet-mixed.

The wet mass is forced through an extruder equipped with screens of size 0.5 mm. The extrudate is spheronized on a friction plate in a spheronizing apparatus. The core material is dried in a fluid bed dryer and classified. The prepared core material is covered by a

separating layer in a fluid bed apparatus with a hydroxypropyl methylcellulose/water solution.

The enteric coating layer is applied to the pellets covered with separating layer from an aqueous dispersion of methacrylic acid copolymer plasticized with triethyl citrate to which a mono- and diglycerides/polysorbate dispersion has been added. The pellets are dried in a fluid bed apparatus.

Example 10:

10

Preparation of enteric coating layered pellets by powder.

Core material

	Magnesium omeprazole	1 500 g
15	Sugar sphere seeds	1 500 g
	Hydroxypropyl methylcellulose	420 g
	Aerosil®	8 g
	Water purified	4 230 g

20 Separating layer

	Core material	500 g
	Hydroxypropyl cellulose	40 g
	Talc	67 g
	Magnesium stearate	6 g
25	Water purified	800 g

Enteric coating layer

	Pellets covered with separating layer	500 g
	Methacrylic acid copolymer	200 g

Triethyl citrate	60 g
Water purified	392 g

5 Magnesium omeprazole, part of the hydroxypropyl methylcellulose and Aerosil® are dry-mixed forming a powder. Sugar sphere seeds (0.25-0.40 mm) are layered with the powder in a centrifugal fluidized coating granulator while spraying a hydroxypropyl methylcellulose solution (6 %, w/w).

10 The prepared core material is dried and covered by a separating layer in a centrifugal fluidized coating-granulator. A fluid bed apparatus is used for enteric coating layering.

Example 11:

Preparation of enteric coating layered pellets with of silicon dioxide seeds.

15

Core material

Magnesium omeprazole	8.00 kg
Silicon dioxide	8.00 kg
Hydroxypropyl methylcellulose	1.41 kg
20 Sodium lauryl sulphate	0.08 kg
Water purified	28.00 kg

Separating layer

Core material	10.00 kg
25 Hydroxypropyl methylcellulose	0.80 kg
Water purified	10.00 kg

Enteric coating layer

Pellets covered with separating layer	300 g
30 Methacrylic acid copolymer	124 g

Polyethylene glycol 400	25 g
Mono- and diglycerides (NF)	3 g
Polysorbate 80	1 g
Water purified	463 g

5

Suspension layering is performed in a fluid bed apparatus. Magnesium omeprazole is sprayed onto the silicon dioxide seeds from a water suspension containing the dissolved binder and a surface active ingredient.

- 10 The prepared core material is covered with a separating layer in a fluid bed apparatus with a hydroxypropyl methylcellulose solution. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, polyethylene glycol 400 and polysorbate is sprayed onto the pellets covered with separating layer in a fluid bed apparatus.

15 Example 12:

Preparation of enteric coating layered pellets.

Enteric coating layer

- 20 Pellets covered with separating layer
(manufacturing and composition

as in example 10) 500 g

Methacrylic acid copolymer 250 g

Polyethylene glycol 6000 75 g

- 25 Mono- and diglycerides (NF) 12.5 g

Polysorbate 80 1.2 g

Water purified 490 g

Example 13:

Preparation of enteric coating layered pellets.

5 Enteric coating

Pellets covered with separating layer 500 g

(manufacturing and composition as in example 1)

Hydroxypropyl methylcellulose phthalate 250 g

Cetanol 50 g

10

Ethanol (95%) 1000 g

Acetone 2500 g

Example 14:15

Preparation of enteric coating layered pellets.

Core material

Omeprazole 225 g

Mannitol 1425 g

20

Hydroxypropyl cellulose 60 g

Microcrystalline cellulose 40 g

Lactose anhydrous 80 g

Sodium lauryl sulphate 5 g

Disodium hydrogen phosphate dihydrate 8 g

25

Water purified 350 g

Separating layer

Core material 300 g

Hydroxypropyl cellulose 30 g

30

Talc 51 g

Magnesium stearate 4 g

Enteric coating layer

Pellets covered with separating layer 300 g

5 Methacrylic acid copolymer 140 g

Triethyl citrate 42 g

Mono- and diglycerides (NF) 7 g

Polysorbate 80 0.7 g

- 10 The dry ingredients for producing the core material are well mixed in a mixer. Addition of granulation liquid is made and the mixture is kneaded and granulated to a proper consistency. The wet mass is pressed through an extruder screen and the granules are converted into a spherical form in a spheronizer. The core material is dried in a fluid bed apparatus and classified into a suitable particle size range, e.g. 0.5 - 1.0 mm. The prepared
- 15 core material is covered with a separating layer and enteric coating layered as described in previous examples.

Preparation of active substance

- 20 Magnesium omeprazole used in some of the examples is produced according to the process described in WO95/01977, the single enantiomers of omeprazole salts are prepared as described in WO94/27988 and omeprazole is produced according to the process disclosed in EP-A1 0005129. These documents are hereby incorporated in a whole by reference.

CLAIMS

1. An oral pharmaceutical dosage form comprising an acid susceptible proton pump inhibitor together with at least one prokinetic agent and optionally pharmaceutically acceptable excipients, characterized in that the dosage form is in the form of a fixed unit dosage form comprising at least two pharmaceutically active components, and wherein the proton pump inhibitor is protected by an enteric coating layer.
2. A dosage form according to claim 1, wherein the dosage form is a tablet formulation.
3. A dosage form according to claim 1, wherein the dosage form is a capsule formulation.
4. A dosage form according to claim 1, wherein the proton pump inhibitor is protected by two layers, an enteric coating layer and a layer separating the enteric coating from the proton pump inhibitor.
5. A dosage form according to claim 1, wherein the dosage form comprises a proton pump inhibitor and one prokinetic agent.
6. A dosage form according to claim 1, wherein the proton pump inhibitor is omeprazole, one of its single enantiomer or an alkaline salt thereof.
7. A dosage form according to claim 6, wherein the proton pump inhibitor is S-omeprazole magnesium salt.
8. A dosage form according to claim 1, wherein the proton pump inhibitor is lansoprazole, one of its single enantiomer or an alkaline salt thereof.

9. A dosage form according to one of claims 6 - 8, wherein the prokinetic agent is mosapride.
10. A dosage form according to one of claims 6 - 8, wherein the prokinetic agent is
5 cisapride.
11. A dosage form according to claim 1, wherein the amount of proton pump inhibitor is in the range of 10-80 mg and the amount of prokinetic agent(s) is in the range of 3-80 mg.
- 10 12. A dosage form according to claim 1, wherein the amount of proton pump inhibitor is in the range of 10-40 mg and the amount of prokinetic agent(s) is in the range of 15-40 mg.
13. A tableted dosage form according to claim 2, wherein the dosage form consists of two separate layers, one layer comprising a proton pump inhibitor and the other layer
15 comprising one or more prokinetic agents.
14. A tableted dosage form according to claim 2, wherein the tablet formulation is a multiple unit tableted dosage form comprising the proton pump inhibitor in the form of enteric coating layered pellets compressed together with a prokinetic preparation into a
20 tablet, whereby the enteric coating layer covering the pellets has mechanical properties such that the tableting of the pellets together with the prokinetic granulation and optionally pharmaceutically acceptable excipients does not significantly affect the acid resistance of the enteric coating layered pellets.
- 25 15. A tableted dosage form according to claim 14, wherein the acid resistance of the enteric coating layered pellets is in coherence with the requirements on enteric coating layered articles defined in the United States Pharmacopeia.

16. A tableted dosage form according to 14, wherein the acid resistance of the enteric coating layered pellets does not decrease more than 10 % during the compression of the pellets into the multiple unit tableted dosage form.

5 17. A tableted dosage form according to claim 14, wherein the enteric coating of the pellets comprises a plasticized enteric coating layer material.

18. A tableted dosage form according to claim 14, wherein the enteric coating layered pellets are further covered with an over-coating layer comprising pharmaceutically
10 acceptable excipients.

19. A tableted dosage form according to claim 14, wherein the tablet is divisible.

20. A tableted dosage form according to claim 19, wherein the tablet is dispersible to a
15 slightly acidic aqueous suspension comprising a prokinetic agent and enteric coating pellets of a proton pump inhibitor.

21. A tableted dosage form according to claim 2, wherein the tablet is an enteric coating layered tablet comprising the proton pump inhibitor surrounded by a layer comprising the
20 prokinetic agent.

22. A tableted dosage form according to claim 14, wherein a multiple unit tableted dosage form comprising the proton pump inhibitor is layered with a separate layer comprising the prokinetic agent, or the multiple unit tableted dosage form is surrounded by
25 a layer comprising the prokinetic agent.

23. A process for the manufacture of a fixed dosage form comprising a proton pump inhibitor and one or more prokinetic agents in a capsule, characterized in that the proton pump inhibitor is prepared in the form of enteric coating layered pellets and the pellets are

filled into a capsule together with the prokinetic agent(s) optionally mixed with pharmaceutically acceptable excipients.

24. A process for the manufacture of a fixed dosage form comprising a proton pump inhibitor and one or more prokinetic agents in a multiple unit tableted dosage form, characterized in that the proton pump inhibitor is prepared in the form of enteric coating layered pellets and these pellets are mixed with prepared prokinetic mixture and optionally pharmaceutically acceptable tablets excipients whereafter the mixture is compressed into a multiple unit tablet without giving any significant change of the acid resistance of the enteric coating layer.

25. A process for the manufacture of a fixed dosage form comprising a proton pump inhibitor and one or more prokinetic agent(s) in an enteric coating layered tablet characterized in that the proton pump inhibitor is admixed with tablet excipients and pre-compressed into a tablet, whereafter tablet is covered with an enteric coating layer and that optionally a separating layer is applied before the enteric coating layer, and the prokinetic agent(s) mixed with pharmaceutically acceptable excipients are thereafter presscoated onto the enteric coating layered tablet.

26. A process for the manufacture of a fixed dosage form comprising a proton pump inhibitor and one or more prokinetic agents in a multiple unit tableted dosage form, characterized in that the proton pump inhibitor is prepared in the form of enteric coating layered pellets and these pellets are mixed with pharmaceutically acceptable tablet excipients and the dry mixture is compressed into a multiple unit tablet without giving any significant change of the acid resistance of the enteric coating layer and whereafter the multiple unit tableted dosage form is spray coating layered by an aqueous suspension of the prokinetic agent(s), or the multiple unit tableted dosage form is layered with a separate layer comprising the prokinetic agent(s) in admixture with pharmaceutically acceptable excipients.

27. A method for the treatment of disorders associated with gastro oesophageal reflux diseases in mammals and man by administering to a host in need thereof a therapeutically effective dose of a multiple unit tableted dosage form according to any of claims 1 to 22.

5 28. A method according to claim 27, wherein the disorder is a gastric disorder associated with gastro oesophageal reflux diseases.

29. Use of a dosage form according to any of claims 1 to 22 for the manufacture of a medicament for treating disorders associated with gastro oesophageal reflux diseases.

10

30. Use according to claim 29 wherein the disorder is a gastric disorder associated with gastro oesophageal reflux diseases.

Fig. 1

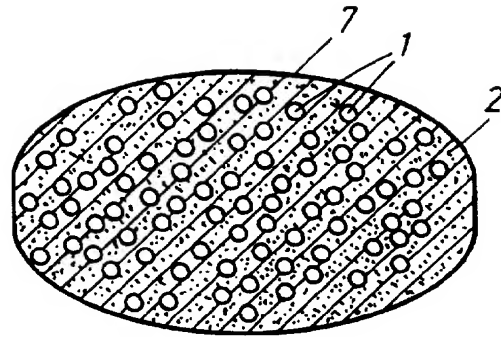


Fig. 2

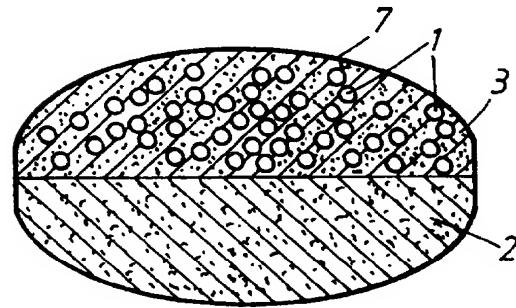


Fig. 3

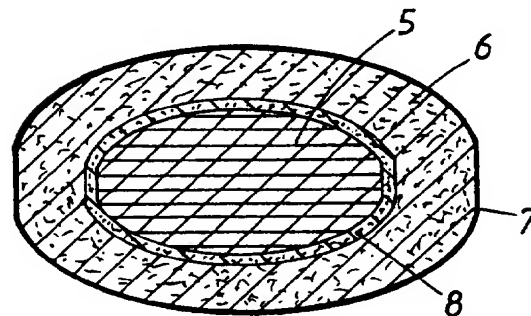
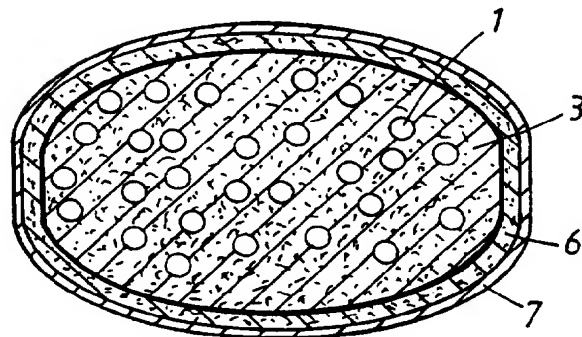


Fig. 4



INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/01736

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 45/06, A61K 31/44, A61K 31/445, A61K 9/20, A61K 9/26, A61K 9/48
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, WPI, WPIL, CLAIMS, USFULLTEXT, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THE NEW ENGLAND JOURNAL OF MEDICINE, October 1995, Alberto Pilotto, M.D. et al: "A Comparison of five maintenance therapies for reflux esophagitis", page 1106, abstract; page 1109, col. 2, line 11-21, line 27-39 --	1-31
A	WO 9501803 A1 (MERCK & CO., INC.), 19 January 1995 (19.01.95), page 2, line 5 - line 29; page 10, line 17 - page 11, line 7 --	1-31
A	EP 0247983 A2 (AKTIEBOLAGET HÄSSLE), 2 December 1987 (02.12.87), page 4, line 25 - line 2; page 8, line 22 - line 32 --	13-31

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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Date of the actual completion of the international search

9 April 1997

Date of mailing of the international search report

22 -04- 1997

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/01736

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0365947 A1 (PHARMACIA AB), 2 May 1990 (02.05.90), page 3, line 41 - line 46; page 4, line 42 - line 57 -- -----	13-31

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/01736

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **27-28**
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Claims 27-28 are directed to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

04/03/97

International application No.

PCT/SE 96/01736

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
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				SU	1820837 A	07/06/93
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				AU	612525 B	11/07/91
				AU	4365089 A	03/05/90
				CA	2000932 A	26/04/90
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				SG	123894 A	17/03/95
				US	5178868 A	12/01/93
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 401/12	A1	(11) International Publication Number: WO 97/41114 (43) International Publication Date: 6 November 1997 (06.11.97)
(21) International Application Number: PCT/SE97/00674 (22) International Filing Date: 22 April 1997 (22.04.97) (30) Priority Data: 9601598-7 26 April 1996 (26.04.96) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): HÖGBERG, Jan-Åke [SE/SE]; Kämpevägen 41, S-151 54 Södertälje (SE). IOAN- NIDIS, Panagiotis [GR/SE]; Ovanbygränd 16, S-163 70 Spånga (SE). MATTSON, Anders [SE/SE]; Kopparvägen 188, S-183 46 Täby (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: PROCESS FOR THE PREPARATION OF A MAGNESIUM SALT OF A SUBSTITUTED SULPHINYL HETEROCYCLE		
(57) Abstract <p>A novel process for the preparation of a magnesium salt of formula (I) of a substituted sulfinyl heterocyclic compound containing an imidazole moiety. The process is carried out by mixing the substituted heterocycle of formula (I) with a weak and a magnesium source. The base and the magnesium source are selected to result in residues which are easy to remove during the reaction. The invention also relates to the use of the produced compounds in medicine.</p>		

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PROCESS FOR THE PREPARATION OF A MAGNESIUM SALT OF A SUBSTITUTED SULPHINYL HETEROCYCLE

Field of the invention.

5

The present invention relates to a novel process for the preparation of magnesium salts of substituted sulfinyl heterocyclic compounds containing an imidazole moiety as well as the use of the produced magnesium salts in medicine. More particularly, the present invention relates to the preparation of magnesium salts of substituted benzimidazoles such as the
10 magnesium salts of omeprazole and of its single enantiomers.

Background of the invention and prior art.

Substituted benzimidazoles such as for instance the compounds with the generic names
15 omeprazole, lansoprazole, pantoprazole, pariprazole and leminoprazole have properties making the compounds useful as inhibitors of gastric acid secretion. This class of compounds is known as proton pump inhibitors or $H^+K^+ATPase$ inhibitors. There are a large number of patents and patent applications disclosing such proton pump inhibitors and processes for their preparation.

20

There is a general need in industry that pharmaceutically active compounds should be produced by processes giving products with properties making them suitable for pharmaceutical preparations, such as being easy to handle in a full scale production and having good storage stability.

25

WO 95/ 01977 discloses a novel magnesium salt of omeprazole with a specific degree of crystallinity making the product suitable for pharmaceutical formulations. The novel product is prepared by a process comprising the following steps; reacting omeprazole with magnesium alcoholate; separating inorganic salts from the reaction mixture; crystallizing
30 the magnesium salt of omeprazole and isolating the product. The magnesium alcoholate is

formed from metallic magnesium which requires special process conditions. The use of magnesium alcoholate in the process constitutes a potential difficulty with the formation of relatively insoluble magnesium salts, such as magnesium hydroxide. Filtration of such magnesium hydroxide is complicated because of gelling and extremely small particle size.

5 The prior process is rather complicated, is water sensitive and requires special conditions. The prior process also has a large equipment requirement in the form of three reaction vessels and a separator. Therefore, there is a need for a more efficient process resulting in shorter manufacturing time, less reaction equipment and giving a higher yield pro volume.

10 The present invention provides improvements over the process disclosed in WO 95/01977 for the preparation of the magnesium salts of omeprazole and of other substituted benzimidazoles. Process for the preparation of certain salts of the single enantiomers of omeprazole, such as the magnesium salts, and processes for their preparation are described in EP 94917244.9.

15 As discussed in WO 95/ 01783 the magnesium salts of proton pump inhibitors, such as the magnesium salt of omeprazole, are especially suitable for the manufacturing of pharmaceutical formulations, such as tablets. The magnesium salts are stable, they may be easily purified by crystallization, and are easy to handle in pharmaceutical procedures and
20 processes.

Summary of the invention.

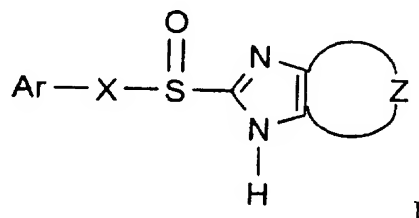
The present invention provides a novel process for the preparation of magnesium salts of
25 substituted sulfinyl heterocycles containing an imidazole moiety and especially of substituted benzimidazole derivatives. The process results in a high yield pro volume, requires less equipment, is less time consuming, environmental friendly and more economically efficient than processes described in the above mentioned patent applications. According to the novel process a magnesium salt of a substituted sulfinyl
30 heterocycle containing an imidazole moiety is prepared by mixing the substituted sulfinyl

heterocycle containing an imidazole moiety with a weak base, preferably an amine or ammonia, and a magnesium source, such as an organic or inorganic magnesium salt or a combination of such salts. By the novel process of the present invention formation of magnesium hydroxide is avoided, for example in the preparation of omeprazole magnesium salt.

Alternatively, the process may also be used to prepare other salts of a substituted sulfinyl heterocycle containing an imidazole moiety, for instance multiple valent salts, such as calcium salts.

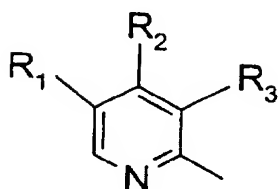
Detailed description of the invention.

The present invention provides a novel method of preparing a magnesium salt of a substituted sulfinyl heterocycle containing an imidazole moiety with the following formula I.

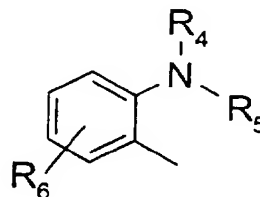


wherein

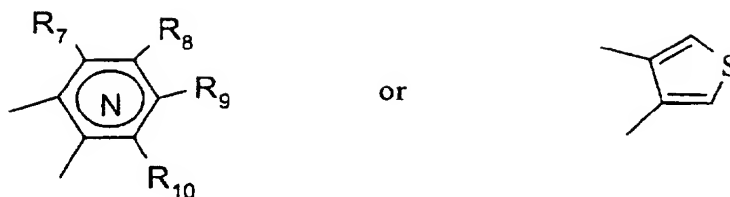
Ar is



or

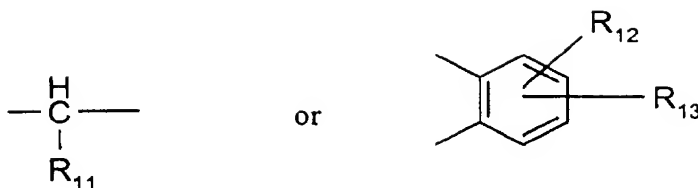


Z is



or

and X is



or

wherein

N inside the benzene ring of the benzimidazole moiety means that one of the carbon atoms substituted by R₇-R₁₀ optionally may be exchanged for a nitrogen atom without any substituents;

R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkylthio, alkoxy optionally substituted by fluorine, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenylalkyl and phenylalkoxy; wherein alkyl and alkoxy groups may be branched or linear and may comprise cyclic alkyl groups such as cykloalkylalkoxi groups.

R₄ and R₅ are the same or different and selected from hydrogen, alkyl and aralkyl;

R₆ is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

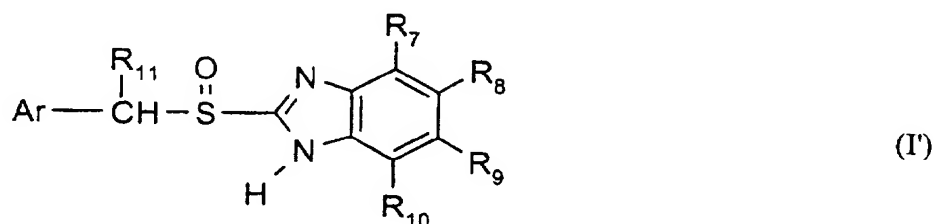
$R_7 - R_{10}$ are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups $R_7 - R_{10}$ form ring structures which may be further substituted;

5 R_{11} is hydrogen or forms an alkylene chain together with R_3 and

R_{12} and R_{13} are the same or different and selected from hydrogen, halogen, alkyl or alkoxy groups, wherein alkoxy groups may be branched or straight $C_1 - C_9$ -chains and the alkyl and alkoxy groups may comprise cyclic alkyl groups, for example cycloalkylalkyl.

10

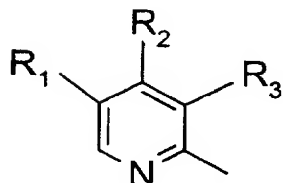
Preferably, the substituted sulfinyl heterocyclic compound containing an imidazole moiety prepared by the novel method is a magnesium salt of formula I'.



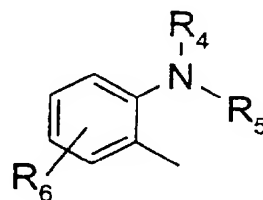
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wherein

Ar is



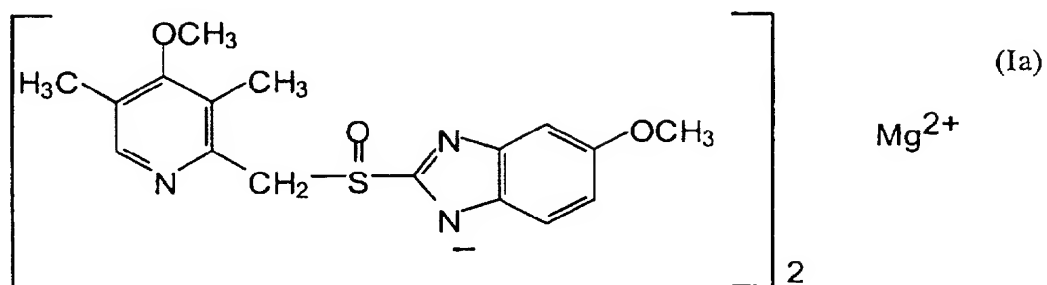
or



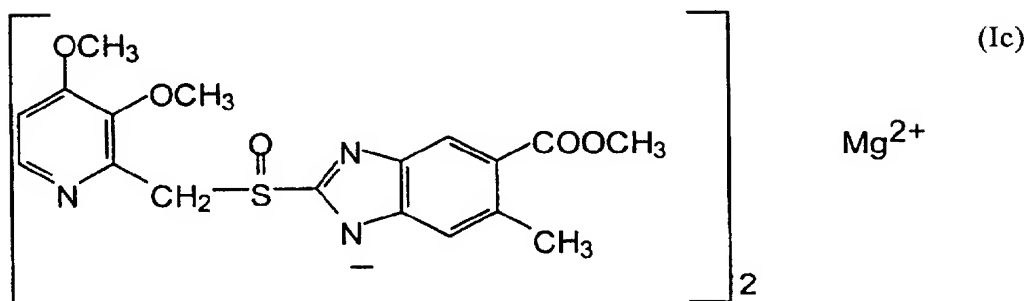
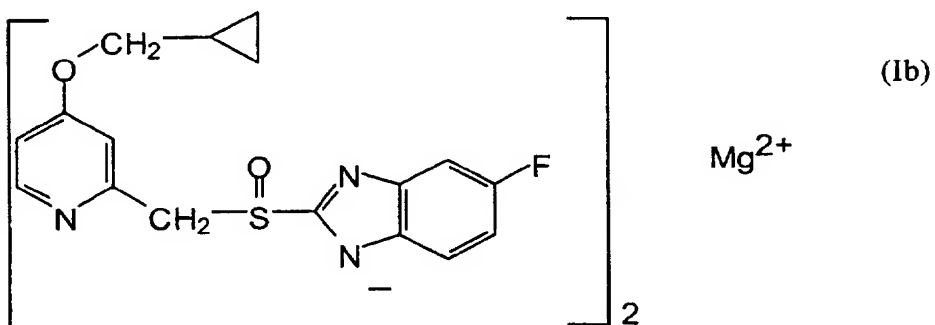
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and $R_1 - R_{11}$ are as defined above in connection with formula I.

Most preferably the compounds prepared by the novel process are any of the formulas Ia to Ih.

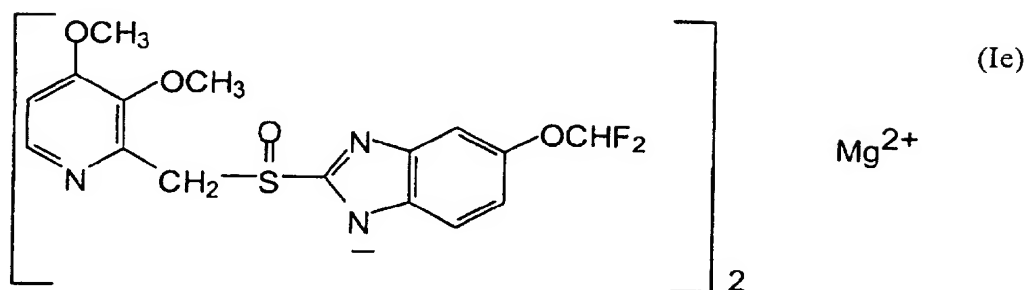
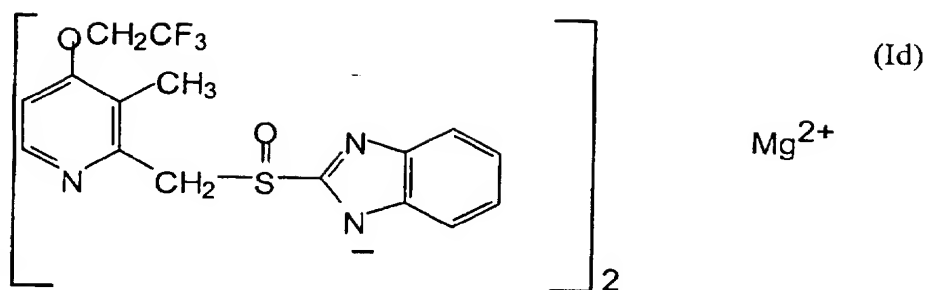


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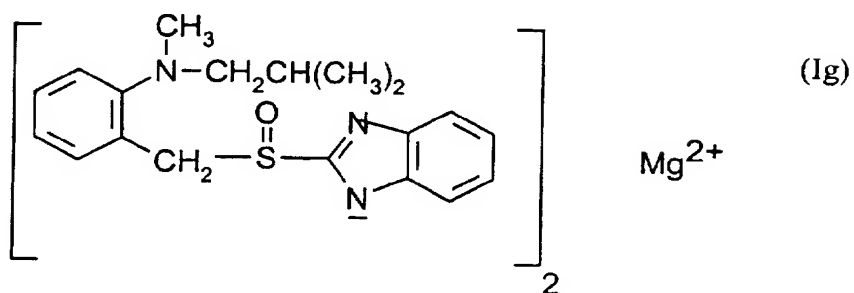
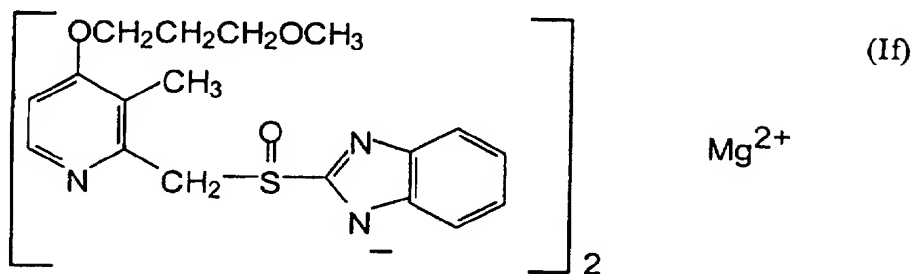


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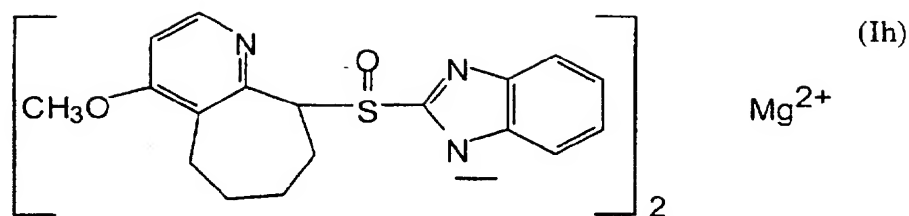
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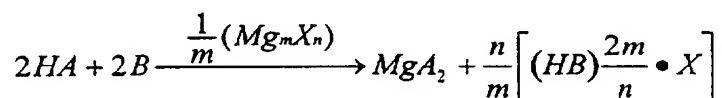


10



The substituted sulfinyl heterocycle of Formula I is mixed/reacted with a weak base and a magnesium source and optionally in the presence of an organic solvent. After the reaction is completed, the mixture is clarified, if needed. The product is preferably precipitated from the filtrate, optionally, by the addition of an appropriate solvent, for instance water or acetone, which facilitates the precipitation of the product. As an additional benefit, when water is used, the solubility of the inorganic salts is enhanced resulting in less impurities in the form of inorganic salts in the obtained product. The obtained product may be further processed by recrystallization.

The novel process according to the present invention may be exemplified by the following reaction scheme showing a reaction between a substituted benzimidazole (HA) and a weak base (B) in the presence of a magnesium source (Mg_mX_n).



In the above formula, wherein HA is a substituted benzimidazole, H denotes the most acidic proton in said compound, B is a weak base and X is a counterion to Mg^{2+} in the magnesium source (Mg_mX_n).

The base used in the reaction must not be toxic or it should only have a low toxicological effect. It shall preferably be a weak base to minimize precipitation of poorly soluble inorganic magnesium salts, such as magnesium hydroxide during the reaction sequence. Such precipitation of, for instance, magnesium hydroxide - is normally difficult to remove during the process and in the final product. With the expression weak base is meant a base with a pKa lower than alkoxides and hydroxides, but higher than the substituted sulfinyl

heterocycles of the present invention, preferably with a pKa from 7-12. More preferably the weak base is an organic amine or ammonia. With respect to environmental aspects the base shall preferably be one resulting in residues in the form of ammonium salts which easily can be isolated, for example by filtration or centrifugation, in order to minimize effluent of nitrogen based pollutants, such as ammonia.

The magnesium source may be an organic as well as an inorganic magnesium salt, such as magnesium acetate, magnesium nitrate, magnesium sulfate, magnesium carbonates and magnesium chloride, preferably magnesium sulfate.

If a solvent is used in the reaction, it is preferably one which can be used throughout the complete process. Such a solvent is preferably an alcohol, for instance methanol.

The process is not temperature sensitive and it may be carried out at ambient temperature.

Of course the process temperature and time may be adjusted with respect to the quality and yield of the obtained product.

The new process according to the present invention may be exemplified in more general terms by the manufacture of omeprazole magnesium salt.

Omeprazole magnesium salt may be formed in accordance with the invention by treating a weight amount of omeprazole with weighed amounts of aqueous ammonia and magnesium sulfate in methanol.

The order of charging the different reactants is not critical for the produced product. A specific order may be preferred with respect to the equipment actually used in the factory.

The temperature may be -10°C to +50°C and preferably is between 0°C and ambient temperature. After termination of the reaction, the resulting inorganic magnesium salts are separated off in a suitable equipment, such as a centrifuge or a pressure filter.

The temperature of the clear solution is adjusted to -10°C to +40°C, preferably 10°C to 35°C. The solution may be seeded with omeprazole magnesium salt crystals and an amount of water is added to start the precipitation. The amount of water is not critical, but can be equal to or less than the volume of the solution; preferably the latter.

The formed crystalline product is separated from the mother liquid (filtrate), for instance by centrifugation or filtration. Other suitable procedures may be used to separate the product. The produced crystalline product is washed with aqueous methanol and dried under reduced pressure and heat.

The process according to the present invention is described in more detail by the following examples, which are not intended to limit the scope of the invention.

Examples

Example 1. Preparation of 5-methoxy-2[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, magnesium salt.

5-Methoxy-2[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (31.6 kg, 91.6 mol) together with aqueous NH₃ (7.4 kg, 107 mol) was added to methanol (212 l). To the obtained mixture MgSO₄ x 7 H₂O (17.6 kg, 69.9 mol) was added at ambient temperature. After the reaction was completed inorganic salts were removed by means of filtration. Water was added to the filtrate, the mixture was clarified and water (91 l) was added. The mixture was kept for stirring in order to crystallize the product. The obtained product was centrifuged and was washed with a mixture of MeOH/water. The product was dried at reduced pressure at 40 °C. Yield: 71%. (Mg content: found 3.47%, Theoretically calculated 3.41%)

The % crystallinity of the obtained product was measured with powder X-ray diffraction (XRD) as described below: A thin layer of the triturated sample was smeared onto a cut silicon single crystal zero background holder which was rotated during the measurement. Cu K α radiation and constant or automatic antiscatter and divergence slits were used to
5 obtain a diffractogram from 1 or 2° 2 θ to at least 35°.

The % crystallinity was calculated with the formula

$$\% \text{ crystallinity} = 100 * C / (A + C)$$

10 C = the area from the peaks in the diffractogram ("the crystalline area"),

A = the area between the peaks and the background ("the amorphous area").

Area calculations were performed between 4-33° 2 θ . The lowest intensity value found in
15 this interval was chosen as the constant background and subtracted from the area A. When constant slits were used the increased background at low angles due to the influence from the primary beam was also subtracted from the area A.

The crystallinity was measured to be 80 \pm 5% (calculation interval 4 - 33°).

20 **Example 2.** Preparation of 5-methoxy-2[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, magnesium salt.

5-Methoxy-2[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (25 g, 72.4 mmol) together with isopropylamine (7.4 ml, 86.9 mmol) was added to methanol (100 ml). To the obtained mixture $\text{MgSO}_4 \times 7 \text{H}_2\text{O}$ (8.85 g, 35.9 mmol) was added at ambient temperature. After the reaction was completed inorganic salts were removed by means of filtration. Water was added to the filtrate, the mixture was clarified and water (100 ml) was added dropwise. The product was filtered off and was washed with a mixture of MeOH/water (50 ml, 1:1). The product was dried at reduced pressure overnight. Yield: 95%. (Mg-content: 3.41; calculated theoretically 3.41).

Example 3. Preparation of 5-methoxy-2[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, magnesium salt.

5-Methoxy-2[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (25 g, 72.4 mmol) together with isopropylamine (7.4 ml, 86.9 mmol) was added to methanol (100 ml). To the obtained mixture $\text{Mg}(\text{OAc})_2 \times 4 \text{H}_2\text{O}$ (9.34 g, 43.6 mmol) was added at ambient temperature. After the reaction was completed inorganic salts were removed by means of filtration. Water was added to the filtrate, the mixture was clarified and water (100 ml) was added dropwise. The obtained product was filtered off and was washed with a mixture of MeOH/water (50 ml, 1:1). The product was dried at reduced pressure overnight. Yield: 92%. (Mg content: 3.42; calculated theoretically: 3.41)

Example 4. Preparation of 5-methoxy-2[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, magnesium salt.

5-Methoxy-2[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (25 g, 72.4 mmol) together with isopropylamine (7.4 ml, 86.9 mmol) was added to methanol (100 ml). To the mixture $\text{Mg}(\text{NO}_3)_2 \times 6 \text{H}_2\text{O}$ (11.2 g, 43.7 mmol) was added at ambient temperature. After the reaction was completed inorganic salts were removed by means of filtration. Water was added to the filtrate, the mixture was filtered and the filter cake was washed with methanol (10 ml). Water (100 ml) was added dropwise to the

combined organic layers. The product was filtered off and was washed with a mixture of MeOH/water (50 ml, 1:1). The product was dried overnight. Yield: 89%. (Mg content: 3.39; calculated theoretically: 3.41))

5 **Example 5.** Preparation of 5-methoxy-2[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, magnesium salt.

5-Methoxy-2[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (1.0 g, 2.9 mmol) together with diethylamine (0.35 ml, 3.4 mmol) were added to methanol
10 (9 ml). To the obtained mixture MgCl_2 (142 mg, 1.5 mmol) in methanol (2 ml) was added at ambient temperature. Water (6.5 ml) was added dropwise. The obtained product was filtered off and was washed with a mixture of MeOH/water (20 ml, 1:1). Yield: 76%. (Mg content: 3.38; calculated theoretically: 3.41)

15 **Example 6:** Preparation of (-)-5-fluoro-2[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, magnesium salt.

(-)-5-Fluoro-2[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (20 g, 57.9 mmol) together with NH_3 (7.5 ml, 100.2 mmol) was added to methanol (80 ml).
20 To the mixture $\text{MgSO}_4 \times 7 \text{H}_2\text{O}$ (11.4 g, 45.3 mmol) was added at ambient temperature. The mixture was clarified. Water (8 ml) was added dropwise during rapid stirring. Another portion of water (72 ml) was added dropwise for 75 minutes. The mixture was stirred for 50 minutes while the product precipitated. The product was filtered off and was washed with a mixture of MeOH/water (2 ml, 1:1). The product was dried at reduced pressure at 35
25 °C overnight. Yield: 61%. (Mg content: 3.40; calculated theoretically: 3.41)

Example 7: Preparation of 5-fluoro-2[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, magnesium salt.

5-Fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (10 g, 28.9 mmol) together with isopropylamine (1.71 g, 28.9 mmol) was added to methanol (40 ml). To the obtained mixture MgCl_2 (1.35 g, 14 mmol) was added at ambient temperature. Excess of amine was evaporated off. The mixture was clarified and water (56.5 ml) was added dropwise. The mixture was cooled to 20 °C and the product was filtered off and was washed with a mixture of MeOH/water (20 ml, 3:1). The obtained product was dried at reduced pressure at 50 °C overnight. Yield: 86%. (Mg content: 3.42; calculated theoretically: 3.41)

Example 8: Preparation of 5-fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, magnesium salt.

5-Fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (690 g, 1.97 mol) together with aqueous NH_3 (140 ml, 2.17 mol) was added to methanol (2.4 l). To the obtained mixture MgCl_2 (105.2 g, 1.08 mol) in methanol (940 ml) was added. The mixture was clarified and water (350 ml) was added during rapid stirring. Another portion of water (3.15 l) was added and the mixture was stirred overnight. The product was filtered off and was washed with a mixture of MeOH/water (1 l, 4:1). Yield: 91%. (Mg content: 3.46; calculated theoretically: 3.41)

Example 9: Preparation of (-)-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, magnesium salt

(-)-5-Methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (10.6 g, 29 mmol) together with aqueous ammonia (3.8 ml of 25%, 50 mmol) was added to methanol (40 ml). To the solution $\text{MgSO}_4 \times 7 \text{H}_2\text{O}$ (5.7 g, 23 mmol) was added. After stirring for 10 minutes the mixture was filtered and the filtrate was diluted with methanol (60 ml). Acetone (150 ml) was added and the solution was seeded with crystals while stirring. After 14 hours the product was isolated by filtration and the

crystals were washed with methanol/acetone (50 ml). The product was dried over night. Yield: 41%. (Mg-content: found 3.33%, Calculated for $(C_{17}H_{18}N_3O_3S)_2Mg$ 3.41%).

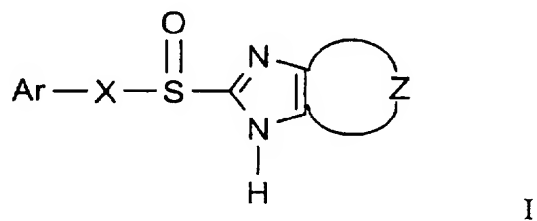
Example 10: Preparation of 5-difluoromethoxy-2-[[[3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, magnesium salt

5-Difluoromethoxy-2-[[[3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (11.1 g, 29 mmol) together with aqueous ammonia (3.8 ml of 25%, 50 mmol) was added to methanol (60 ml). To the solution $MgSO_4 \times 7 H_2O$ (5.7 g, 23 mmol) was added. After stirring for 3 minutes the mixture was filtered. Water (40 ml) was added dropwise to the filtrate while stirring. After 30 minutes the product was isolated by filtration and the crystals were washed with methanol/water (25 ml). The product was dried under reduced pressure. Yield: 67 %. (Mg-content: found 3.07%, Calculated for $(C_{16}H_{14}N_3O_4S)_2Mg$ 3.08%).

The best mode to practice the invention at present is by the process described in Example 1.

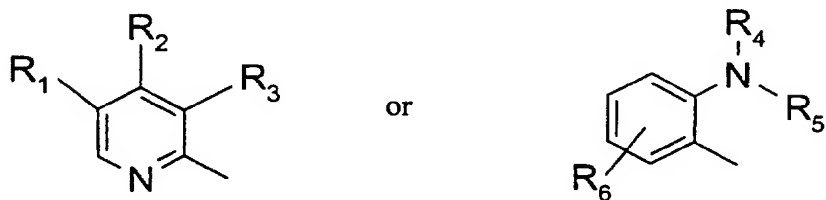
CLAIMS

1. A process for the preparation of a magnesium salt of a substituted sulfinyl heterocyclic compound containing an imidazole moiety according to Formula I

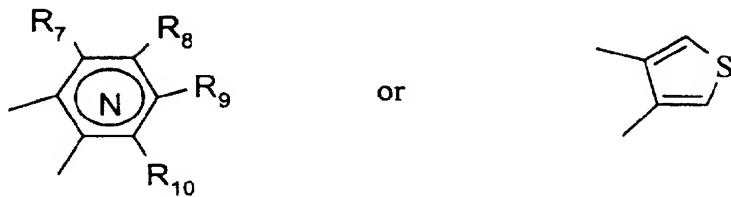


wherein

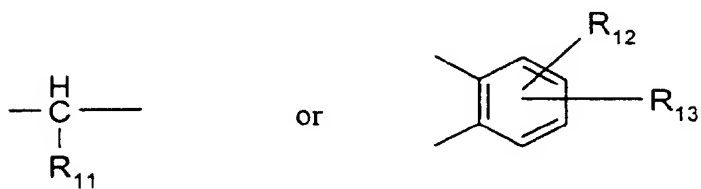
Ar is



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and X is



wherein

N inside the benzene ring of the benzimidazole moiety means that one of the carbon atoms substituted by R₇-R₁₀ optionally may be exchanged for a nitrogen atom without any
5 substituents;

R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkylthio, alkoxy optionally substituted by fluorine, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenylalkyl and phenylalkoxy, wherein alkyl and alkoxy groups may be branched
10 or linear and may comprise cyclic alkyl groups such as cykloalkylalkoxi groups;

R₄ and R₅ are the same or different and selected from hydrogen, alkyl and aralkyl;

R₆ is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;
15

R₇ - R₁₀ are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R₇-R₁₀ form ring structures which may be further substituted;

20 R₁₁ is hydrogen or forms an alkylene chain together with R₃ and

R₁₂ and R₁₃ are the same or different and selected from hydrogen, halogen, alkyl or alkoxy groups, wherein alkoxy groups may be branched or straight C₁-C₉-chains and the alkyl and alkoxy groups may comprise cyclic alkyl groups, for example cycloalkylalkyl,
25

wherein the substituted sulfinyl heterocycle of Formula I is mixed together with a weak base and a magnesium source.

2. A process according to claim 1, wherein the weak base is selected from the group of
30 organic amines and ammonia.

3. A process according to claim 1, wherein the weak base is ammonia.
4. A process according to claim 1, wherein the magnesium source is selected from the group of organic and inorganic magnesium salts.
5. A process according to claim 1, wherein the magnesium source is selected from the group of magnesium acetate, magnesium nitrate, magnesium sulfate, magnesium carbonates and magnesium chloride, preferably magnesium sulfate.
6. A process according to claim 1, wherein the reaction is carried out in the presence of a solvent.
7. A process according to claim 1, wherein the reaction is carried out in the presence of an aqueous organic solvent.
8. A process according to claim 1, wherein the weak base and magnesium source are selected to give an ammonium salt which can be removed by filtration during said process.
9. 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, magnesium salt prepared by a process according to any of claims 1 - 8.
10. (-)-5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, magnesium salt prepared by a process according to any of claims 1 - 8.
11. A pharmaceutical composition comprising a magnesium salt of a substituted sulfinyl heterocycle of formula I prepared by a process according to any of claims 1 - 8 as an active ingredient and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/00674

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 401/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9601623 A1 (ASTRA AKTIEBOLAG), 25 January 1996 (25.01.96)	1-8
X	--	9-11
A	WO 9501977 A1 (ASTRA AKTIEBOLAG), 19 January 1995 (19.01.95)	1-8
X	--	9, 11

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

5 June 1997

Date of mailing of the international search report

07 -08- 1997

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International application No.

PCT/SE 97/00674

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

20/05/97

International application No.

PCT/SE 97/00674

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9601623 A1	25/01/96	AU 2993795 A	09/02/96
		CA 2170647 A	25/01/96
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